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A Journal of Neurology

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PART I., VOL. 36.

PARASYPHILIS OF THE NERVOUS SYSTEM.[1]

BY JAMES McINTOSH AND PAUL FILDES,
HENRY HEAD AND E. G. FEARNSIDES.

From the Wards and from the Bacteriological Laboratory of the London Hospital (Professor William Bulloch, F.R.S.).

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The following preliminary communication is based upon several lines of work, carried out simultaneously in the wards, and in the bacteriological laboratory of the London Hospital. Each separate research will form later the subject of a paper in this Journal, but we thought it wiser to give a preliminary account of our general conclusions before presenting the various more special and detailed communications.

The results embodied in this paper are based entirely on cases where the serological examinations have been carried out by Dr. Fildes and Dr. McIntosh and the clinical records compiled by Dr. Head and Dr. Fearnsides.

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[1] This paper was laid before the Neuropathological Section of the International Medical Congress on August 12, 1913.

We have the greatest pleasure in thanking first of all Professor Bulloch, in whose laboratory the work was carried out. Our thanks are also due to the staff of the London Hospital, more particularly to Dr. J. H. Sequeira and Dr. Cecil Wall, for the unrivalled opportunities they so generously gave us for examining patients under their care. If, however, the name of no physician is mentioned in the report of a case, it may be assumed that the patient was under the care of Dr. Head.

CHAPTER I.—CLINICAL CHARACTERISTICS OF PARASYPHILIS.

The conception of parasyphilis as a morbid process, responsible for a wide series of clinical manifestations, was first formulated by Fournier [8] in 1894 to account for cases, obviously of syphilitic origin, which were not amenable to antisyphilitic treatment. "Ce néologisme," he says, "que je dois à un savant helléniste specifie bien, paraît-il, étomologiquement le caractère des accidents en question, dont le propre est de procéder originairement de la syphilis sans être pour cela cependant syphilitique de nature." He believed that this peculiar post-syphilitic condition was able to evoke a series of diseases, all of which might exist otherwise apart from antecedent syphilis. His conception was thus essentially a clinical one, transferred by implication into the field of pathology.

Fournier did not restrict the term parasyphilis to such diseases as dementia paralytica and tabes dorsalis alone, but believed that some cases of progressive muscular atrophy, epilepsy, infantilism, Little's disease, imbecility, and even certain forms of neurasthenia were all manifestations of the activity of the "parasyphilitic" process. Gradually, however, though the truth of Fournier's conception of the post-syphilitic nature of some of these conditions has been generally acknowledged, the range of activity of parasyphilis of the nervous system has tended to become restricted to tabes dorsalis and dementia paralytica; but at the same time an increasingly large number of complications have been described as occurring in the course of these two diseases.

Thus Dejerine [4] has described the pathological changes associated with muscular atrophy, arising in the course of tabes dorsalis, and Nonne [25] looks upon all cases of primary optic atrophy, which follow syphilis, as an incipient stage of the same disease. Mott [18] thinks it probable that Erb's spinal paralysis and certain cases of amyotrophic lateral sclerosis may be primary post-syphilitic dystrophies; optic atrophy he looks on as one with tabes dorsalis and dementia paralytica.

Fournier's original view was revived by A. Read Wilson [34] but both the clinical and serological reports in his paper lacked sufficient fulness to support his conclusions.

(1) *Clinical Forms assumed by the Disease.*

Year by year the line, once so firmly drawn between tabes dorsalis and dementia paralytica, grew fainter as soon as the identity of the pathological process underlying the two diseases was recognized. With the invention of the term "tabo-paresis" the boundaries between the two diseases fell; it was recognized that manifestations characteristic of each might occur together in the same patient, and their validity as anything more than convenient terms for groups of signs and symptoms disappeared for ever.

Let us then consider the various phenomena which may make their appearance in the course of dementia paralytica and tabes dorsalis, that is to say, the clinical conditions universally recognized to be due to parasyphilis of the nervous system :—

Dementia and other mental states characterized by destruction of mental capacity; all forms of epileptiform convulsions and attacks; defective reactions of the pupil; ptosis and ocular paralyses of all kinds; paralyses in the territory of other cranial nerves, such as the trigeminal and facial; paresis or paralysis of the lips, tongue, palate, and larynx; primary optic atrophy; ataxy and inco-ordination; tremor of various kinds; muscular atrophy, which appears as a rare manifestation in otherwise classical cases of tabes dorsalis; paresis of both cerebral and spinal origin; lateral sclerosis; various disturbances of sensation; visceral attacks, such as gastric crises; the most diverse conditions of the reflexes ranging in the case of the knee-jerks from exaggeration to complete abolition; sphincter affections and disturbances of the detrusor action of the bladder.

Now, it is only by arbitrary selection that these diverse signs and symptoms can be said to constitute two diseases. We shall attempt to show that they are all manifestations of a syphilitic state which can produce innumerable combinations of signs and symptoms, according to the parts which happen to be attacked. We shall also show that a patient, who at first developed one group of signs, may later exhibit other signs which, on the old nomenclature, would have carried him into another category.

Like all other syphilitic affections of the nervous system, "parasyphilis" is a widespread abnormal condition, and the clinical forms assumed by the disease depend solely on the parts attacked at the moment.

(a) Progressive Muscular Atrophy.

Dejerine [4] laid stress in 1889 on the frequent occurrence of muscular atrophy in tabes dorsalis, and attributed it to peripheral neuritis; he placed the incidence as high as 20 per cent. Although few would set the proportion as high, atrophy of spinal origin is a familiar complication of undoubted tabes dorsalis, and French authorities have long recognized it as a manifestation of parasyphilis (Kinnier Wilson [35]).

Fournier [9] insists that uncomplicated muscular atrophy may be parasyphilitic, basing his opinion on cases observed by Raymond [32], in one of which an autopsy was obtained. This revealed lesions of the spinal meninges, degeneration of the anterior roots, loss of cells in the anterior horns with profound endarteritis obliterans of the vessels. Raymond describes the condition as a vascular myelitis, showing nothing specific and resembling in no way the lesions of tertiary syphilis.

Fournier insists that these patients do not benefit even from the most drastic anti-syphilitic treatment, and points out that clinically the wasting is preceded by lancinating pains.

Mott [18] mentions that some forms of amyotrophic lateral sclerosis may be parasyphilitic, but cites no instances. Most German and English writers ascribe these cases to the direct action of syphilis, and do not consider the possibility that they may be parasyphilitic. Thus, Nonne [22] speaks of a meningomyelitis with participation of the anterior horns in the diffuse affection. He quotes amongst others both Raymond's and Dejerine's cases, but does not discuss their relation to parasyphilis.

On the other hand, A. Read Wilson [34] gathered together a series of cases of muscular atrophy, partly from the literature and partly from his own observation, in which the Wassermann reaction was positive in the serum, and classes them all as parasyphilis, oblivious of the extreme difficulty in differential diagnosis.

Now, there can be little doubt that in the majority of cases where syphilis is responsible for muscular atrophy, the condition is caused by a true syphilitic meningomyelitis. For not only are these patients peculiarly susceptible to treatment with salvarsan or neo-salvarsan, but other signs are usually present pointing to a diffuse lesion of the spinal cord and its membranes. The following case is a good instance of muscular atrophy due to cervical meningomyelitis of syphilitic origin.

Case 36.—Rose C., aged 36. [Dr. F. J. Smith.] She was married in 1900, but left her husband three years later because he would not work. No definite history of infection could be obtained. She had never been pregnant.

In 1909 she suffered for four weeks from intense headache, which ultimately passed away entirely.

In December, 1910, she had a "stroke," her speech became affected, and she was unable to walk steadily. Since then her memory has deteriorated and she has been unable to work.

In January, 1912, her right hand began to waste, and she lost power so rapidly that, by June of the same year, she was unable to hold a knife. This wasting was thought at another hospital to be due to cervical ribs, and in July a rib was removed, but she steadily grew worse. In September the left hand became affected. Ever since the middle of 1912 she has been occasionally unable to control her motions and hold her water.

In November, 1912, she first came under our observation. Her speech was slurred and her memory defective. The pupils reacted to light, but the contraction was not maintained and tended to be rhythmic; on accommodation the reaction was normal. Her face was expressionless, and on the left side there was slight weakness of its lower half. The tongue moved well and was not tremulous. The fundi showed no abnormal appearances.

All the muscles of both hands, of both forearms, and to a less degree, of the arms, were considerably wasted, especially on the left side. The muscles of the shoulder-girdle were much less affected. Both lower extremities were slightly spastic.

No hyperalgesia or loss of sensation could be discovered, even in the arms. The knee-jerks were exaggerated; ankle-clonus was obtained on both sides and both plantar reflexes gave an extensor response.

She had considerable difficulty in holding her water and could not control her motions if they were soft.

The Wassermann reaction was:—

Serum	4.4.4.4.2.[1]
Cerebrospinal fluid	4.4.1.0.0.

---

[1] Throughout this investigation we record the results of the Wassermann reaction in this form. The test is quantitative and falling doses of serum and cerebrospinal fluid are used. Formerly we followed the usual method of recording the reaction and represented complete inhibition by + + + + and incomplete inhibition by + + +, + + or +. To economize space these would now be written 4, 3, 2, or 1. The figures 4.4.4.4.4 imply that the reaction was complete in each of the five dilutions, whilst 4.4.4.0.0 shows that the reaction was complete in the first three, but negative in the last two dilutions. Such results as 2.0.0.0.0 or 1.0.0.0.0 have no diagnostic value. The figures above the line always refer to the serum, those below the line to the cerebrospinal fluid.

But in the following case the picture was one of a typical muscular atrophy, complicated only by the defective reaction of the pupils.

Case 75.—William H., a married man, aged 36, began to lose power in the middle finger of his right hand two years ago (1911). About three months later wasting started in the left arm, and within the space of a year had progressed to such an extent that he was unable to use either arm.

On admission in March, 1913, all movements were impossible in the right upper extremity below the shoulder-joint, and all the muscles, especially those of the hand, showed intense wasting. He could slightly flex the ring finger of his left hand, and evoke a feeble contraction of the flexors of the elbow, but otherwise all muscular power was lost in the left arm. All movements of the right shoulder-girdle were lost; he could slightly contract the muscles of the left shoulder, but not with sufficient strength to produce any material change in the position of the limb. All the muscles of the neck were weaker than normal, and somewhat wasted.

The knee-jerks were brisk, ankle-jerks were easily obtained, and the plantar reflexes gave a flexor response.

He had suffered no pain, and no disturbance of sensibility could be discovered.

The pupils reacted extremely feebly to light, but reacted well to accommodation. The tongue showed no fibrillary tremor, and the movements of the palate and larynx were unaffected.

At no time had he experienced any trouble in holding or passing his water.

He was in the Army in 1896, and again between 1900 and 1908; but although exposed to infection, he can remember no venereal disease of any kind. But in spite of this complete absence of knowledge of infection, the Wassermann reaction was as follows:—

Serum	4.4.4.4.4.
Cerebrospinal fluid	4.4.4.0.0.

The cells were 44 per cubic millimetre.

Here, then, is a patient who differs from the usual cases of muscular atrophy due to syphilitic meningomyelitis in the absence of pains, of spastic signs, and in the integrity of the mechanism of micturition. At no time had there been any intercurrent manifestation which could be attributed to syphilitic vascular lesions in other parts of his nervous system.

On the other hand, this patient differed from a true case of progressive muscular atrophy in the defective reaction of the pupils, and in the presence of a positive Wassermann reaction in the cerebrospinal fluid; we are, therefore, inclined to believe that he is an example of parasyphilis amyotrophica. For had he been simply an instance of progressive muscular atrophy in a patient suffering from syphilis, the reaction would have been negative and not positive in the cerebrospinal fluid.

(*b*) *Epileptic Manifestations.*

Fournier [10] called attention to a form of epilepsy, liable to appear many years after infection with syphilis, which was entirely refractory to antisyphilitic treatment. This, he believed, to be a manifestation of parasyphilis. He points out that syphilitic encephalopathy, accompanied by epileptiform convulsions, is characterized by the co-existence of other phenomena, pointing to a gross lesion of the brain, and rapidly produces other signs and symptoms indicative of cerebral syphilis. He insists that it runs its course with greater or less rapidity towards recovery or death, and that cerebral syphilis is peculiarly amenable to antisyphilitic treatment, even though complete recovery may not occur. But epilepsy of parasyphilitic origin tends to appear as an isolated symptom, and continues in this form without the addition or conjunction of other cerebral manifestations; it may last over a long period, and is refractory to antisyphilitic treatment; bromide does not produce a cure, but may moderate the frequency and severity of the attacks.

Nonne [23] entirely agrees with this description and accepts parasyphilitic epilepsy as a condition comparable to tabes dorsalis and dementia paralytica. He carefully differentiates it, on the one hand, from cerebral syphilis, and, on the other, from the seizures which may herald the early stages of dementia paralytica. It arises suddenly in later middle life, and continues for many years, resisting all antisyphilitic treatment.

The following case, where parasyphilitic epilepsy arose on a basis of congenital infection, illustrates the long duration of the disease, and is particularly interesting from the presence of Argyll-Robertson pupils.

Case 66.—Florence G., an unmarried woman, aged 24, has been under the care of H. H. for epileptiform attacks since September, 1904. In 1900, at the age of 11, she developed fits which have continued ever since, in spite of treatment. The attacks come on without warning, she passes water, falls, and has not infrequently hurt herself. Throughout she is completely unconscious and sleeps after the attack. Usually two or more fits occur in rapid succession.

Her memory and attention are poor, but she shows no gross signs of dementia. Her speech is unaffected, and, excepting after an attack, she is not liable to headaches or vomiting. She is somewhat deaf; the corneæ show faint nebulæ, but the fundi are unaffected. The pupils are usually equal and of fair size, but they do not react to light; they react well to accommodation. Otherwise no affection can be discovered in the territory of the cranial nerves. The knee-jerks and other reflexes, including the plantars, are normal, except after a series of convulsions. Motion, sensation, and the action of the sphincters are entirely unaffected.

She is short and broad, 4 ft. 10 in. (146 cm.) in height, with a narrow forehead and pegged teeth. Scars are visible at the angles of the mouth, and she has the appearance of a case of congenital syphilis.

In June, 1913, the Wassermann reaction was as follows:—

Serum	4.4.2.0.0.
Cerebrospinal fluid	4.4.4.4.0.

The cells were 40 per cubic millimetre.

Such reactions are incompatible with the diagnosis of uncomplicated congenital syphilis and point definitely to infection of the central nervous system. At the same time there are no signs of any affection of the meninges or spinal cord, and we believe this patient is an instance of parasyphilitic epilepsy.

(c) *Lateral and Combined Sclerosis.* (*Erb's Syphilitic Spinal Paralysis.*)

An incomplete transverse myelitis is universally recognized to be the commonest form of syphilitic disease of the spinal cord. This myelitis is a diffuse inflammatory and vascular disturbance, bearing all the marks of a direct hyperplastic reaction to the infection.

But in 1892 Erb [6] suggested that syphilis might produce degeneration of the long paths, such as the pyramidal tracts, not as a consequence of interruption by inflammatory foci, but as a direct effect exercised by the poison upon them. For many years doubt has been thrown on the existence of such tract degenerations, in consequence of the extreme difficulty in differentiating clinically between the results of a diffuse meningomyelitis and those produced by primary degeneration of the posterior and lateral columns of the cord. In both cases the signs may consist solely of increased knee-jerks, ankle-clonus with extensor plantar reflexes, more or less spasticity, and ataxy, with loss of recognition of posture and passive movement in the lower extremities.

However, there can now be little doubt that primary degeneration of the lateral, with or without degeneration of the posterior columns, may occur as a consequence of syphilitic infection. Nonne [24] sums up an admirable discussion of the question in the following conclusions: (1) It is certain that cases exist which show exactly the signs and symptoms described by Erb; (2) this disease may be caused by several anatomically distinct conditions. It may be due to a true combined degeneration or to a degeneration of the long tracts caused by a chronic myelitis or meningomyelitis with more or less vascular disease.

Meanwhile, the idea was growing up that possibly Erb's spinal paralysis might be of parasyphilitic origin. But, in view of the extreme difficulty in making a differential diagnosis during life, this view remained a tentative suggestion.

We believe that these cases of lateral or combined sclerosis, however closely they may resemble one another clinically, may be based pathologically either on syphilitic inflammation or so-called "parasyphilitic" degeneration. More commonly, they are the expression of tertiary meningeal and vascular changes; under these circumstances they will probably respond to antisyphilitic treatment, and at the same time the Wassermann reaction in the cerebrospinal fluid will rapidly diminish and may even become negative. A large number of these patients with late meningomyelitis at one time or another show signs of some root-lesion; these signs, although of extreme differential importance in diagnosis, not uncommonly pass unobserved, as they do not obtrude themselves on the patient's consciousness. We believe that the following case is an example of this condition:—

Case 91.—Dennis K., labourer, aged 36. In 1904 he contracted syphilis and suffered from a chancre, rash, and sore throat, for which he was treated with mercury by the mouth for twelve months.

In 1907 he developed gummatous ulcers on his shins, which healed rapidly under the administration of iodides.

On January 4, 1912, he was taken ill with dizziness, pains in his belly, and repeated vomiting. This attack was followed by headache which lasted till his admission in July, 1912.

About four weeks before admission, a pimple appeared on his palate which enlarged, broke down, and led to a perforation into the nose.

On admission (July, 1912), his mental state was unaffected, but he suffered from severe headache. The knee-jerks were brisk and both plantars gave an extensor response. He walked well and was not ataxic, but both great toes tended to remain in the extended position. There was no loss of muscular power.

Distinct hyperalgesia was present in the region of the eighth and ninth thoracic roots on both sides, but no sensory change could be discovered elsewhere to any test. The pupils reacted well, and the movements of the face, tongue and palate were normal. He had a little difficulty in beginning micturition, but no other sphincter trouble.

The Wassermann reaction was :—

Serum	4.4.3.0.0.
Cerebrospinal fluid	4.4.4.1.0.

He was given 0·6 grm. of salvarsan intravenously on July 10, 1912, and a similar dose on the 17th. By January 15, 1913, the reaction had become :—

Serum	3.2.1.0.0.
Cerebrospinal fluid	1.0.0.0.0.

At the same time the headache and hyperalgesia around the trunk disappeared and his general condition improved strikingly.

This is a characteristic instance of degeneration of the lateral columns of the cord, depending on a chronic meningomyelitis.

Compare with this case the following one, which we believe to be an instance of parasyphilis.

Case 71.—William H., labourer, aged 54. He denies all infection with syphilis, but in 1875, at the age of 17, and again in 1878, aged 20, suffered from gonorrhœa. Neither attack was accompanied by a sore, rash, or other secondary manifestation of syphilis.

In 1907, his eyesight began to fail, and in 1910, his legs became stiff and his gait unsteady.

When admitted to the hospital in February, 1912, his mental state was normal, his speech unaffected, and he had not suffered from fits or any other attacks.

His gait was spastic, but there was no paralysis or loss of muscular strength. He tended to sway slightly with his eyes closed, but did not fall.

The knee-jerks were exaggerated, ankle-clonus was obtained, and the plantar reflex gave an extensor response on both sides.

There was no gross loss of recognition of posture and passive movement, and he responded well to the tuning fork tests. Sensation to touch, pain, heat and cold was entirely unaffected.

Both pupils reacted readily to light and accommodation in spite of his defective vision.

Vision in both eyes was very poor, and the letters of the test types could not be distinguished at six metres. The discs were pale with a distinct lamina cribrosa and clear edges.

No other special senses were affected.

Face, tongue, and palate moved normally.

He had difficulty in passing his urine, and on admission, he was suffering from overflow from a distended bladder.

The Wassermann reaction was :—

Serum	4.3.2.0.0.
Cerebrospinal fluid	4.4.4.3.0.

Cells were 12 per cubic millimetre.

The contrast between these two cases is striking. In D. K. (Case 91) the infection was definite and was followed by undoubted secondary manifestations; twelve years later he developed a gumma of the palate with headache, signs of lateral sclerosis and of an irritative lesion of thoracic nerve-roots. He improved greatly under salvarsan, and the Wassermann reaction in the cerebrospinal fluid fell rapidly. In fact he was a typical instance of tertiary meningomyelitis.

In W. H. (Case 71), on the other hand, the infection was doubtful, and, as in so many cases of tabes dorsalis, was followed by no secondary manifestations. The whole infection ran its course under cover of a gonorrhœa. Nearly thirty years later, he first began to lose his sight from primary optic atrophy, and a little later developed the signs of lateral sclerosis. The Wassermann reaction was positive in serum and cerebrospinal fluid.

(*d*) *Optic Atrophy.*

In the consideration of primary optic atrophy, we are faced by exactly the opposite problem to that in the case of the primary tract degenerations. It appears so frequently as an accompaniment to tabes dorsalis that its parasyphilitic origin is universally acknowledged, even when it occurs alone. Thus Nonne [25] goes so far as to say that primary optic atrophy is almost always a manifestation of tabes dorsalis, and not infrequently may exist alone for a long period before the appearance of other signs of the disease.

Yet he gives [26] a perfect instance of a woman whom he had watched for eighteen years with primary optic atrophy, and no signs of tabes dorsalis or dementia paralytica had so far appeared.

Case 186.—Jane A., a widow, aged 60. In 1875, at the age of 22, she married her first husband, who died six years later from asthma and bronchitis; two out of three children, the issue of this marriage, are alive and well. In 1892 she was married again to a husband who ultimately developed dementia paralytica and died insane in 1912. In this marriage she had two children, the first of whom, born in 1893, died of wasting at three months old, whilst the second, born two years later, is living and healthy.

In 1905 she began to suffer from pains in the chest, but in view of the large gastric ulcer from which she ultimately died, these pains are of doubtful significance.

In 1907 she began to lose her eyesight. This loss of vision progressed slowly and culminated in 1910 in complete blindness.

When admitted in May, 1913, she was a sallow, anæmic woman, extremely intelligent, but totally blind. She suffered mainly from hæmatemesis and malæna, which were due to a large chronic ulcer of the stomach.

She showed no loss of memory or attention, and had had no seizures or fits of any kind.

Her speech was unaffected.

There was no tremor, no ataxy, and she did not become unsteady when her eyes were closed. No loss of sensation could be discovered to touch, pain, or temperature, and she was able to appreciate perfectly the vibrations of a tuning fork. Recognition of posture and passive movements was unaffected.

The knee-jerks and ankle-jerks were normal, and both plantar reflexes gave a flexor response.

She was completely blind and the discs were in a condition of primary white atrophy. Hearing, smell and taste were unaffected. The pupils were equal and reacted well to accommodation. They did not react to light in consequence of her blindness. All movements of the eyes, face, tongue, palate, and larynx were performed normally. The sphincters were unaffected.

The Wassermann reaction was :—

Serum	4.4.3.0.0.
Cerebrospinal fluid	4.4.3.0.0.

The cells were 30 per cubic millimetre.

She died suddenly on May 30, 1913, of hæmatemesis, and at the *post-mortem* examination, a large chronic ulcer of the stomach was found, which had opened one of the coronal arteries. The brain and spinal cord showed no signs of gummatous meningitis, and we believe that she was a case of parasyphilis optica.[1]

We have already described a case of parasyphilitic lateral sclerosis with primary optic atrophy (Case 71, p. 10), and it will, perhaps, be worth quoting an instance of optic atrophy with loss of knee-jerks, observed over a period of ten years.

Case 131.—Edward R., aged 52. In 1885, at the age of 24, he developed a chancre, followed by a rash and a sore throat. He was treated for six weeks only, but remained in perfect health.

In 1895, at the age of 34, he went blind from primary optic atrophy, and has been under the care of H.H. for the last ten years. From the beginning, his knee-jerks and ankle-jerks have been absent, but he has shown no signs of ataxy, tremor, or defects of speech. We have never been able to discover any disturbance of sensation.

In August, 1911, he had a sudden attack of confusion with loss of memory, which passed away and left him in his previous condition. With this exception he has not progressed, and is in the same state in which he was first seen ten years ago.

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[1] A complete account of the *post-mortem* examination will be published later.

The Wassermann reaction in September, 1911 was :—

Serum	4.4.2.1.0.
Cerebrospinal fluid	4.4.4.3.1.

and the cells were in excess.

Similar cases occur repeatedly in the literature and there can be no difference in principle between them and the rare instances where the knee-jerks and other deep reflexes happen to be normal.

No one can therefore doubt that primary optic atrophy can occur as a parasyphilitic phenomenon, alone, or in combination with primary degeneration of the lateral or posterior columns of the spinal cord.

(2) *Clinical Antecedents.*

The first essential factor in the development of parasyphilis seems to be time. In many cases, where the affection of the nervous system is a manifestation of active syphilitic changes, the first symptoms occur within ten years of infection. An analysis [13] of 33 cases in males, where the date of infection was known, showed an average of two years and eight months.

On the other hand, in 38 cases of tabes dorsalis seen by H. H. in private practice, where the date of infection could be determined accurately, the first symptom, usually consisting of pains, appeared on an average after an interval of fourteen years. The average of 11 hospital cases in males, observed by ourselves, where the signs of disease were characteristic and the Wassermann reaction was strongly positive in the cerebrospinal fluid, also gave an average period of fourteen years.

Secondly, in a large proportion of cases of parasyphilis, the primary and secondary manifestations have been extremely slight. Thus, out of 40 undoubted cases of tabes dorsalis seen in private practice, all infection with syphilis or gonorrhœa was denied in 3[1]; gonorrhœa only had existed in 9, whilst 13 had suffered from a chancre without any secondary manifestations. All of these 13 patients were under careful medical treatment, and it is unlikely that a rash, sore throat or fall of hair would have escaped observation. Thus, out of 40 cases of tabes dorsalis 25, or 62 per cent., showed at most a primary sore in consequence of infection.

Amongst 15 hospital patients with tabes dorsalis in whom the Wassermann reaction was strongly positive, both in the serum and cerebrospinal fluid, 3 denied all venereal disease, but acknowledged frequent exposure; one had suffered from gonorrhœa only, whilst in 5 a chancre had been present followed by no secondary manifestations. Here again in 60 per cent. a primary sore had been the maximum consequence of infection.

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[1] One of these patients had lived with a woman who developed syphilis. He was carefully examined at the time by experts who could find no trace of any venereal disease in him.

The third peculiarity, which is revealed by the study of cases of undoubted parasyphilis, is the apparent want of correspondence between the efficiency of the treatment in the early stages of syphilis and the appearance of parasyphilitic disease. Many of the men seen in private practice had been treated by the highest authorities in this country and abroad; mercury may have been given by the mouth for three or even more years, they may have been to Aachen year after year, and yet tabes dorsalis appeared, exactly as in the hospital patient who had at most "taken medicine" for a few weeks. Moreover, the form of the disease and the frequency of its occurrence does not vary materially in the different European countries amongst those who have been exposed to infection, in spite of the diverse methods of treatment in vogue.

Chapter II.—The Wassermann Reaction.

(1) *In Syphilis and Parasyphilis of the Central Nervous System.*

With the discovery by Wassermann and Plaut [33] that the cerebrospinal fluid reacted positively in cases of dementia paralytica, a problem was stated, to which the answer is still uncertain. Innumerable examinations have been made and columns of statistics compiled by laboratory workers who knew little or nothing of the source of the fluid they were investigating, beyond the diagnosis of the disease; in many cases the cerebrospinal fluid had even been sent from hospitals or asylums at a distance. But, as Plaut [29] himself points out, the difficulties in differential diagnosis, particularly between active syphilitic disease of the brain and parasyphilis cerebralis, are often extreme; one falsely diagnosed case of this kind may ruin a column of statistics, and we believe that want of accuracy and fulness in the clinical examinations of patients, from whom serum and cerebrospinal fluid has been withdrawn, is responsible for much of the confusion which exists at present. The time for collecting mass statistics is over, and each case must be investigated with as much care as if it were to be published separately. This we have attempted to do; we have included no case that has not been examined by one of us and where every note has not been taken by ourselves.

The form of the Wassermann reaction we have employed has been evolved during the last five years in the course of general diagnostic work in several thousand cases of all forms of disease. It differs from the so-called "original method," as finally described in 1913 by Plaut [30], in the following particulars:—

(*a*) The fixation stage is carried out with more concentrated constituents.

(*b*) The cerebrospinal fluid is used in greater quantity and *unheated.*

Thus we use 0·2 c.c. of the fluid in 1 c.c. during the fixation stage of the reaction, while the "original method" employed 0·2 c.c. of *heated* cerebrospinal fluid in 3 c.c. In the so-called "Auswertungsmethode" 1 c.c. of cerebrospinal fluid is used in 3 c.c.

(*c*) A heart cholesterin antigen is used [16].

(*d*) The complement is standardized against a constant quantity of amboceptor.

(*e*) Every case is tested quantitatively by titration of the serum and cerebrospinal fluid.

During the last fifteen months we have examined by this method 372 cases where the diagnosis of syphilitic infection was made by Dr. J. H. Sequeira, and verified by continuous observation of the patients.

The results were as follows:—

Primary syphilis	... ...	93	per cent. positive.
Secondary ,,	... ...	99	,, ,,
Tertiary ,,	... ...	97	,, ,,
Congenital ,,	... ...	100	,, ,,

Only one apparently non-syphilitic individual gave a positive reaction, a case of acute malaria twenty-four hours after the rigor.

As a control on the method employed, we investigated thirty-two cases of gross nervous disease in patients in whom there was no reason to suspect the presence of syphilis, and did not find a single instance in which either blood or cerebrospinal fluid reacted positively. These included eight cases of cerebral tumour; five cases of vascular lesions of the brain, such as embolism, thrombosis, and hæmorrhage; five cases of disseminated sclerosis, two cases of spinal tumour, three cases of other chronic spinal cord conditions, three cases of peripheral neuritis, and three cases of neurasthenia.

As a further control of our clinical observations we examined twenty cases of undoubted syphilis, without obvious signs pointing to affection of the central nervous system. In every case the serum was positive and the cerebrospinal fluid negative. At the same time we have observed a certain amount of delay in the hæmolysis of the cerebrospinal fluids of patients with secondary syphilis, and in view of the results of Altmann and Dreyfus [1], and Max Fraenkel [11], we accept the occasional occurrence of a positive reaction in the cerebrospinal fluid of patients with secondary syphilis.

The serological results obtained by us in cases of gross disease of the central nervous system of syphilitic origin can be tabulated shortly as follows:—

	Number of cases	Positive reaction in	
		Serum	Cerebrospinal fluid
Dementia paralytica and tabo-paresis	17	17	17
Tabes dorsalis	24	20	22
Cerebrospinal syphilis—			
(*a*) With involvement of the spinal cord	23	22	21
(*b*) Without involvement of the spinal cord	25	22	7

Now it is obvious that these results agree in some respects with those of previous workers, whilst in other directions they differ fundamentally.

In dementia paralytica our figures correspond with those published in the literature, although the number is too small to disclose the rare occurrence of negative reactions in the cerebrospinal fluid. Among the twenty-four cases of tabes dorsalis, two gave a negative reaction in the cerebrospinal fluid; both these patients were in a completely stationary condition. Thus, in tabes dorsalis the reaction may be diminished or lost in consequence of fluctuations in the activity of the disease, a factor which is not present as far as we know in dementia paralytica.

Such diminished activity may be due either to the long period during which the disease has lasted, or perhaps occasionally to the severity of the anti-syphilitic treatment.

In progressive cases the reaction is almost uniformly positive, both in the serum and cerebrospinal fluid.

Although the strength of the reaction is usually less in comparison with that found in dementia paralytica, nevertheless in the cerebrospinal fluid of patients with tabes dorsalis, it is often very strong and little reliance can be placed upon the strength of the reaction for the purposes of differential diagnosis.

When we turn to the results obtained by us in cerebrospinal syphilis, they differ considerably from those recorded in the literature.

According to Plaut [31] "Sowohl bei Lues cerebri als bei Lues spinalis ist die negative W. Reaktion des Liquor die Regel. . . .

Dieses Verhalten findet sich in gleicher Weise bei allen Formen der Erkrankung. . . ."

Nonne [27] gives as a typical result in the fluid of cerebrospinal syphilis :—

"(*a*) Originalmethode (0·2 c.c.) positiv in ca. 10. Proz.

"(*b*) Höhere Liquormengen fast stets positiv."

This remark dealing with the quantity of test fluid refers to the "Auswertungs-Methode" of Hauptmann and Hössli [12], according to which five times the ordinary quantity of cerebrospinal fluid is used. This method gives a much larger number of positive reactions than the "original method," especially in cerebrospinal syphilis, but the majority of these positive results are obtained with the larger quantities of fluid only; thus it is clear that in Nonne's view the strength of the reaction in cerebrospinal syphilis is slight. He says [27] "Ist die Wassermannsche Reaktion schon nach der Originalmethode (0·2 c.c. des zu untersuchenden Liquors) positiv"—that is if the reaction is strong—"so besteht die grosse Wahrscheinlichkeit, dass es sich bei dem vorliegenden Fall um eine Paralyse oder Taboparalyse handelt, weit seltener um eine Lues cerebrospinalis oder um eine reine Tabes."

However, as will be seen from our figures, this view appears to be untenable. We have formed the opinion that there is a great difference between cases of syphilis of the central nervous system according to whether the spinal cord itself is affected or not. This difference is found both in the incidence of the reaction and in its strength. We have found that in "spinal" cases the reaction is not only constant in the cerebrospinal fluid but also strong, certainly as strong as that found in dementia paralytica. In "cerebral" cases, on the other hand, the reaction is much less constant and is quantitatively weak. We therefore dispute the suggestion, that either the occurrence of the reaction in the fluid or its strength has an obvious bearing upon the differential diagnosis between dementia paralytica and cerebrospinal syphilis.

As has already been pointed out by Assmann [2] and by Plaut, the purely endarterial forms of cerebral syphilis tend to give negative reactions in the cerebrospinal fluid more frequently than the meningeal. We have also further observed that a positive reaction in the purely cerebral forms is more frequent, though feeble, when the test is applied shortly after the onset of the symptoms.

The great outstanding difference between the reaction in "parasyphilis" and cerebrospinal syphilis is the prompt effect of antisyphilitic treatment upon the latter condition. The strong reaction in the cerebrospinal fluid of a case of meningomyelitis may be rapidly reduced or made negative by salvarsan injections, while the same treatment appears to have much less effect, if any, in dementia paralytica, and very little in tabes dorsalis. It is therefore absolutely essential in every case to determine the amount of treatment to which the patient has been subjected before a serological investigation is interpreted.

As an example of the different behaviour of the Wassermann reaction under treatment in syphilis and parasyphilis, we may instance the following cases:—

Chronic Spinal Meningitis (*Case 91*)—

	Serum	Cerebrospinal fluid
July 10, 1912	4.4.3.0.0.	4.4.4.1.0.
Two doses (0·6 grm.) of salvarsan.		
January 15, 1913	3.2.1.0.0.	1.0.0.0.0.

Tabes Dorsalis (*Case 37*)—

	Serum	Cerebrospinal fluid
October 8, 1912	4.4.2.0.0.	4.4.3.1.0.
Two doses (0·9 grm.) of neo-salvarsan.		
May 7, 1913	4.4.4.2.0.	4.4.2.0.0.

We may summarize our results as follows:—

In dementia paralytica and tabo-paresis a strong reaction is almost constant in both serum and cerebrospinal fluid. The presence of a negative reaction would make a diagnosis of these conditions highly improbable.

In tabes dorsalis the reaction is almost constantly positive in serum and cerebrospinal fluid, except when the activity of the disease has subsided as a result of time or treatment. The strength of the reaction is often not so great as that in dementia paralytica; on the other hand, this is in no way a constant rule. Thus, a negative reaction obtained during an active stage of a suspected case of tabes dorsalis would render the diagnosis unlikely.

In untreated cerebrospinal syphilis, the reaction in the spinal fluid varies according to the site of the lesion. When the spinal cord and its meninges are affected, the reaction is positive and usually very strong; but when the signs indicate that the cord has escaped, it is inconstant, and, when present, weak. The reaction is most often positive when the lesions are recent. In treated cases, the reaction is positive in the cerebrospinal fluid according to the efficiency or otherwise of the treatment.

(2) *The Origin of the Wassermann Reaction in the Cerebrospinal Fluid.*

In order to discuss the origin of this reaction and its behaviour under various conditions, it will be necessary to consider the researches of Turnbull upon the subarachnoid space and the deductions drawn therefrom by Fildes. These views differ considerably from those usually taught.

We believe that the subarachnoid space is a closed cavity, potential in the cranium and actual in the spinal canal. It is filled with a relatively stagnant cerebrospinal fluid, which acts simply as a water cushion to the spinal cord and brain-stem.

The cerebrospinal fluid serves no lymphatic function and is shut off from the lymphatics of the brain, cord and roots by the endothelium covering the walls of its containing space.

The origin of the cerebrospinal fluid is unknown; but in all probability it is a secretion of the endothelium lining the subarachnoid space. It is doubtful to what extent the ventricular fluid contributes to its constitution, and we think it is improbable that this fluid passes directly from the ventricles into the cerebrospinal fluid by way of the foramen of Magendie, even when this exists. Normally the cerebrospinal fluid in the cranium is a mere film of moisture lubricating the opposing walls of the subarachnoid space as in a joint cavity; in the spinal canal it collects in some bulk and remains in a relatively stagnant condition. Under abnormal circumstances the quantity of fluid may be increased, and, when degenerative or inflammatory conditions of the pia are present, unusual substances may contaminate it as an exudate. Even when the pia is unaffected, such substances as the endothelium is capable of secreting may find their way into the fluid.

The Wassermann substance is not capable of passing an intact membrane, and it will only appear in the spinal fluid when the pial covering is diseased. The source of the Wassermann substance throughout the body is a syphilitic focus; it probably represents one of the elements derived from a cell which has been specifically affected by the *Spirochæta pallida*. Its source, therefore, in the central nervous system will be either a meningeal and vascular focus in cerebral syphilis or a "parasyphilitic" focus in parasyphilis. An acute or chronic meningitis will obviously involve the pia mater, and the products of this process, including the Wassermann substance, will pass into the cerebrospinal fluid; thereaction will therefore be positive. If, however, the lesion is purely thrombotic, and the meninges are little affected, the

Wassermann substance will not pass into the fluid to any great extent. The reaction in the cerebrospinal fluid may therefore be negative or slightly positive only. Further, it must be remembered that the test fluid is collected from a site far distant from the brain and that, if there is any interruption to a free passage of the fluid from the brain to the spinal cord, Wassermann bodies, poured into the cerebral subarachnoid space, may not reach the lumbar region. In this manner we endeavour to explain the fact, that in a purely cerebral lesion, whether meningeal or not, the cerebrospinal fluid usually yields a negative reaction, while, when the cord is affected, it is positive. Now a gummatous process is known to be peculiarly susceptible to salvarsan treatment; such a lesion therefore may be rapidly healed and the pia reduced to a normal condition. That is to say, both the source of the Wassermann bodies and the opportunity for their entry into the fluid may be readily abolished. In such cases, therefore, the Wassermann reaction should rapidly become negative in the fluid, and this we have shown to be the case (*vide* pp. 10 and 18.)

Turning to the consideration of parasyphilis, we hold that the origin of the reacting substance is the "parasyphilitic" lesion which, as we show later, is situated in the nervous tissue. This substance does not find its way into the fluid by means of any of the "normal" channels which have been described, but passes up the adventitial lymphatics to the pia. This pial membrane is always diseased in dementia paralytica and tabes dorsalis, and thus the reacting substance can pass into the cerebrospinal fluid. But this Wassermann reaction cannot be made negative by treatment under ordinary conditions, because antisyphilitic remedies circulating in the blood-stream cannot obtain access to those essential tissues of the central nervous system, which form the "parasyphilitic" focus (*vide infra*, p. 27). The process will therefore continue unhindered to give rise to the substance responsible for a positive Wassermann reaction in the cerebrospinal fluid.

CHAPTER III.—A THEORY OF PARASYPHILIS.

(1) *The Pathological Anatomy of Parasyphilis.*

Parasyphilis of the nervous system is a widespread condition, which may affect every structure in the brain and spinal cord. If we wish to study the anatomical changes with which it is associated, it is useless to examine long-standing cases of such a disease as tabes dorsalis; the essential lesions have long given place to chronic conditions, which reveal little of the nature of the original reaction. But a study of the spinal cord in cases of tabo-paresis, where the patient has been killed by the cerebral lesions, at a time when those in the spinal cord are still fresh, throws more light on the nature of the fundamental processes.

According to the views widely adopted at the present time, parasyphilis of the nervous system depends on an atrophy of the nerve-fibres and cells, associated with a cellular infiltration of the meninges and adventitial sheaths of the vessels and proliferation of the neuroglia. The majority of the authorities look upon the degeneration of the essential nervous structures as primary, and the vascular and glial proliferation as a secondary sclerosis. Some, however, have urged that, at any rate in tabes dorsalis, the degeneration is secondary to changes in the meninges and adventitial sheaths of the vessels.

On the other hand, the lesion of chronic syphilitic meningitis (gummatosis) appears to be of a different nature; it starts as a lymphocytic accumulation about a small vessel, the lumen of which tends to become obliterated by proliferation of its endothelium. The accumulation of plasma cells and fibroblasts then leads to the formation of a definite granuloma. Any degeneration of nerve-fibres or cells which may occur is produced by interference with the blood-supply or pressure of the inflammatory tissue.

We have elaborated the view that, in all the lesions of active syphilis, the interstitial reaction is the same in quality, and differs only in the relative number of the reacting cells. Everywhere the activity of the spirochæte is manifested about itself as it lies in the neighbourhood of a capillary. There occurs a reaction of the fixed cells and a reaction of the wandering cells, producing a localized collection, or series of collections of lymphocytes, and later of plasma cells and fibroblasts. The same sequence is discoverable in chancres, papules and gummata, and the gross appearance of the lesion is dependent merely upon the amount of thrombosis and fibrosis. In those organs which contain a specialized parenchyma, a reaction may also occur in these cells, and the result will be degeneration followed by more or less recovery; the amount of this recovery will depend on the extent to which these specialized cells possess the power of regeneration.

The differences between the microscopical anatomy of the changes which occur in chronic syphilitic meningitis and in "parasyphilis," are generally supposed to represent a fundamental difference in the nature of the pathological process. Nevertheless, in our view there is no such essential difference between the two conditions from a pathological aspect. We look upon a "parasyphilitic" lesion as a reaction and not as a degeneration; it is a reaction to the same toxic influence, the *Spirochæta pallida*, as that which evokes a gumma. But in the one case the chief reaction occurs in the nerve-cells (parenchyma of the brain) and neuroglia, whilst in the other the chief reaction occurs in the meninges and vessels (interstitial tissues of the brain). Parasyphilis of the brain or cord therefore corresponds to the parenchymatous lesions of the testicle (so-called parasyphilis of the testicle), while the gummatous lesions of the brain correspond to gummatous (interstitial) orchitis.

When a spirochæte, as shown by Noguchi [21], appears in the nervous tissues, there is a double reaction: firstly of the nerve-cells (parenchyma) and neuroglia (fixed interstitial cells); and secondly, of the wandering cells. These latter may be observed in large numbers, lymphocytes and plasma cells, filling the lymph spaces of the meninges and perivascular sheaths; but they are largely prevented from reaching the actual site of the spirochæte by the peculiar anatomical configuration of the part. They lie within the adventitial sheath of the vessels and are excluded from the nerve-tissues proper by this sheath, which is a continuous uninterrupted boundary, an extension of the limiting membrane of Lenhossek, between the nerve-tissues and the vessels. Thus, although the fixed elements, nerve-cells and neuroglia will react locally, the wandering cells remain distant and diffuse, and no "gumma" will be formed. As regards the nerve-cell itself, the reaction must entail a certain amount of death and degeneration.

Thus, a "parasyphilitic" disease is not due to a simple degeneration of nerve-elements, but is a reaction, affecting all the tissues which lie within the brain and spinal cord, and does not differ in pathological essentials from the reaction in chronic syphilitic meningitis. What then is the essential nature of a reaction which can manifest itself in such various anatomical changes as "gummatosis" and "parasyphilitic" disease?

(2) *The Nature of the Toxic Action in Parasyphilis.*

Mott [19] believes that this condition is in the strictest sense a non-specific sequel to syphilitic infection; the nerve-elements have reacted over a long period to the poison, and, in the attempt, fall victims to exhaustion and early death. The changes in neuroglia and lymphatic channels are consequent on the necrosis of the cells and fibres and are a secondary expression of the same toxic activity.

The remarkable tendency of some strains of syphilis to infect the nervous system led many, especially the French authorities, to postulate a "Syphilis à virus nerveux." With the final recognition that tabes dorsalis and dementia paralytica demanded syphilis as an antecedent condition, the discussion as to the existence of a nerve-poison in some brands of infection shifted somewhat. Investigators began to suggest that some syphilitic infections might carry with them a peculiar liability to evoke parasyphilitic disease, and the notorious tendency of tabes dorsalis to follow mild primary manifestations was used as an additional support to this supposition. Cases were described [17] where one woman infected several men, all of whom developed parasyphilis; and Brosius [3] placed on record the story of seven glass-blowers who caught the disease from the same fellow workman; four out of five, who were examined twelve years later, were affected with nervous disease thought to be parasyphilitic.

Neisser [20] pays little attention to the question of parasyphilis but says: "Es kann wohl kein Zweifel darüber bestehen, dass, in der Pathogenese dieser Krankheiten die Syphilis zwar das wichtigste, ja sogar wohl unerlässliche ursächliche Moment darstellt, aber nicht das einzige. Sicherlich gehören entweder bestimmte ererbte Prädispositionen, oder bestimmte anderweitige Schädigungen (Alkohol) dazu, um bei Syphilitikern Tabes und Paralyse zu erzeugen, falls man nicht die Hypothese, dass es ein spezifisches Nervenvirus gibt, akzeptieren will." Thus it is obvious that, although he accepted tertiary manifestations as a striking evidence of the extent to which the mode of reaction of the tissues had been changed ("Umstimmung"), he did not think that it bore materially on the phenomena of parasyphilis.

With von Pirquet's conception of "allergie," a line of thought was opened which led McIntosh and Fildes to formulate the view we hold with regard to the nature of parasyphilis. Von Pirquet showed that all infections led to a change in the character of the reaction of the tissues to the poison. This might take place in two directions; they might respond less and less to infection ("hypoallergie"), until at last they ceased to respond altogether and became "anergic." But, on the other hand, a change in the opposite direction might occur; the reaction might appear both more quickly and with greater violence to a smaller dose of the poison. This he spoke of as "hyperallergie" and brought into this category the phenomena, described by Richet, under the name of "anaphylaxis."

Von Pirquet had no opportunity of working on the manifestations of syphilis in the light of this conception, but he quotes Finger and Landsteiner as showing that the period of incubation of a second infection can be shortened, and that patients with tertiary syphilis may react locally to the injection of syphilitic material.

In our view tertiary and "parasyphilitic" phenomena are manifestations of hypersensitiveness ("hyperallergie"), which reaches its extreme form in anaphylactic shock. As the tissues are hypersensitive, they react more strongly to a minute dose of the poison, and hence some of the difficulty of discovering the spirochæte in gummatous and parasyphilitic tissues.

The difference between the anatomical consequences, produced by the impact of the poison in the two cases, depends on the nature of the tissue attacked. Thus, gummatosis is the reaction of hypersensitive vessels and connective tissue, parts which tend to show proliferative changes. On the other hand, the pathological anatomy of "parasyphilis" of the central nervous system is the expression of the response of hypersensitized, highly differentiated nerve-elements which have no power of regeneration. The profound difference between the two forms of disease-process depends, not on the extent to which the tissues have become hyperallergic, but on the fact that, in the one case, proliferative repair can occur at once, whilst, on the other hand, the injury to the nerve-elements results in their death. This view explains the fact that "parasyphilitic" processes occur in those nerve-fibres in which the sheath of Schwann is absent. This structure is not only an essential factor in the process of regeneration, but also, no doubt assumes a nutritive or protective rôle, to such an extent that a reaction which is sufficient to destroy a nerve-fibre not provided with this sheath may be insufficient to injure to any considerable extent the nerve protected by the neurilemma.

This theory also accounts for the occasional presence in the same patient both of gummatous meningitis and of "parasyphilitic" degeneration; the one is the reaction of a highly sensitized connective tissue, whilst the tabetic changes are the expression of a similar condition in the long fibres of the posterior columns.

On this view we can also explain the peculiar course of the milder forms of parasyphilis. The tendency of many cases of tabes dorsalis is to run on somewhat acutely to a certain stage and then to stop, frequently for many years. This is particularly well seen where the first manifestation takes the form of primary optic atrophy, which leads invariably to complete blindness; but from that time onwards the patient may remain free from any further affection until, perhaps many years later, his knee-jerks disappear, or he suffers from some cerebral complication.

(3) *How is the Central Nervous System rendered Hypersensitive to the Spirochæte?*

In order that a part of the body may be rendered hypersensitive, it must have been exposed previously to the influence of the toxic agent. Thus, a patient who has had tuberculosis may be rendered so hypersensitive to the organism that minute and otherwise harmless doses, even of tuberculin, applied at a later date, will produce an immediate reaction. In the same way, the tissues of a syphilitic patient become hypersensitive, so that a reapplication of the virus from without or the recrudescence of spirochætes within, will produce a large reactive lesion (syphilitic pseudo-chancre, gumma) out of all proportion to the number of spirochætes present. The central nervous system, also, may be sensitized, and the reappearance of spirochætes at a later date then produces an exaggerated reaction either in the nerve-tissues proper or in the vascular tissues of the nervous system. How then can this sensitization of the central nervous system be brought about under the influence of syphilitic infection?

According to the extensive researches of Orr and Rows [28], the perineural lymphatic space, which surrounds every spinal nerve and extends along the roots to the pia mater, is the afferent lymphatic channel of the central nervous system, while, according to Turnbull, the lymph spaces of the pia, which are in connection with these perineural sheaths, are also direct continuations of the adventitial lymph spaces of the perforating vessels. Thus we hold the view, that the space within the adventitial sheath of the finest capillary is in direct continuity, by means of lymph spaces, with the lymphatics of the spinal nerves, and that substances, ascending such nerves (Orr and Rows), will be brought into intimate relation with the nerve-tissues of the central nervous system.

Further, both Ehrmann [5] and Levaditi [14] have shown that the *Spirochæta pallida* may pass from a primary sore up the peripheral nerves; they discovered the organism not only in the lymph spaces of the perineurium, but actually between the nerve-fibres. It may, therefore, be assumed that the *Spirochæta pallida* is equally capable of affecting the cutaneous nerves during the secondary period, and hence the central nervous system, especially that part related to the afferent peripheral nerves (posterior roots), will come under the influence of spirochætes or their toxins, from the whole superficies of the body and most of the internal organs. Thus, the posterior columns, which are in direct lymphatic connexion with the posterior roots, may be sensitized by the toxins of spirochætes ascending the afferent peripheral nerves; our explanation of the regional sensitization in tabes dorsalis corresponds to that given by Orr and Rows for the changes they have described in the posterior columns as a consequence of bed sores.

To explain the manifestations of dementia paralytica we again follow the views of Orr and Rows; sensitization of the essential tissues of the brain may arise from an affection of the lymph system of the cranial nerves by spirochætes or their products. It is possible, however, that in some cases sensitization may follow an infection of the intracranial tissues during the secondary period. A considerable amount of clinical and pathological evidence has now been collected to show that a meningitis is not uncommon in the acute stage of syphilis. Should this infection lead to the spread of spirochætes amongst the essential tissues of the brain, it would doubtless leave them, equally with the meninges, in a hypersensitive condition.

If now a spirochæte which has remained dormant, or has been active in some indifferent part of the body, appears among these sensitized nervous tissues, two different phenomena may be observed according to the site of its activity. If within the lymphatic area of the posterior columns, a violent reaction may ensue, injuring the nerve-fibres and producing proliferation of the neuroglia and wandering cells. The injury to the nerve-fibres will lead to degeneration, and this will continue as far as the reflection of the neurilemma and no further. When this stage has been reached, the process is at an end so far as concerns this particular region; in this sense tabes dorsalis is not a progressive degenerative lesion.

If the renewed activity of the spirochæte, however, happens to occur in the cerebrum, a similar reaction will take place in the nervous and other tissues, but, owing to the greater diffuseness of the sensitization, the area affected will tend to be greater. All intrinsic fibres within the sphere of reaction will tend to degenerate, but the process can seldom be observed to the end, owing to the involvement of vital functions and the early death of the patient.

The "parasyphilitic" reaction need not, however, be confined to these two areas. Isolated collections of cells, for instance those of the anterior horn, may be affected and give rise to "parasyphilitic" muscular atrophy. Other groups of fibres or cells, alone or in combination, may be involved in the reaction according to the site of reappearance of the spirochæte, and so determine the clinical manifestations in each case of parasyphilis.

It will be recognized that antisyphilitic treatment can have no direct effect upon such degenerating nerve-structures, and therefore upon the symptoms and signs of tabes dorsalis or dementia paralytica; nevertheless, it may prevent the occurrence of a further reaction in another area by killing the spirochætes.

The fact, however, that antisyphilitic treatment has little or no effect upon the Wassermann reaction in dementia paralytica and in tabes dorsalis, must be explained on other grounds. It is possible that the degeneration of the nerve tissues continues the type of the initial reaction, and is thus "specific," giving rise continually to the Wassermann body. On the other hand, a more probable explanation is to be found in the fact that antisyphilitic remedies do not readily obtain access to spirochætes lying in the nerve-tissues; indeed, W. H. Willcox [quoted in 15] has already demonstrated that, after treatment with salvarsan, though all the viscera contained large quantities of arsenic, it was entirely absent from the brain.

If, then, the focus of origin of the Wassermann substance lies within the essential tissues of the central nervous system, it will not be exposed to the action of antisyphilitic remedies, and will remain active in spite of treatment. Thus, the cellular infiltration of the meninges, dependent on the activity of this focus, will also remain unaffected by treatment and will determine that injury of the pial covering which allows the passage of the Wassermann substance into the cerebrospinal fluid.

"Parasyphilis," as we have endeavoured to show, depends upon an anaphylactic reaction in the tissues of the central nervous system, which have been rendered hypersensitive in accordance with their peculiar lymphatic distribution. "Parasyphilis," therefore, does not differ from "chronic cerebral syphilis" in any essential pathological particular. It is merely a similar reaction in a different tissue. The word "parasyphilis" suggests a concept which is entirely foreign to our view of the nature of these morbid processes; it should therefore be confined solely to the multifarious clinical manifestations which may arise from the reaction of hypersensitive nerve-tissues and neuroglia to the *Spirochæta pallida*.

Conclusions.

(1) Parasyphilis of the nervous system is a purely clinical conception. It is a diseased state which may affect any part of the brain or spinal cord; the manifestations of tabes dorsalis and dementia paralytica can only be erected into two clinical divisions by an arbitrary selection of signs and symptoms. Some forms of progressive muscular atrophy, lateral and combined sclerosis, primary optic atrophy and periodic epileptiform attacks may be equally definite manifestations of parasyphilis.

(2) Parasyphilis is slightly, if at all, amenable to antisyphilitic treatment with compounds of arsenic and mercury, probably because these bodies do not enter the essential structures of the central nervous system.

(3) Parasyphilitic states are peculiarly liable to arise after mild syphilitic infection. Sixty per cent. of cases of tabes dorsalis have suffered from at most a primary sore, and in many instances the whole course of the initial infection was run under cover of a gonorrhœa.

(4) In dementia paralytica and in active, untreated cases of tabes dorsalis and tabo-paresis, the cerebrospinal fluid yields a positive Wassermann reaction, often of great strength.

(5) With acute or chronic syphilis of the nervous system, other than parasyphilis, the behaviour of the cerebrospinal fluid depends upon the extent to which the spinal cord and its membranes, including those of the brain-stem, are affected. Thus, most cases of meningomyelitis show a strong positive reaction in the cerebrospinal fluid, whilst cerebral lesions tend to give a weakly positive or even a negative reaction.

(6) Antisyphilitic treatment has a profound effect on the positive reaction in syphilitic meningomyelitis, and the cerebrospinal fluid may give a negative reaction after a few months.

But in cases of parasyphilis no obvious change occurs in consequence of such treatment, within any comparable period.

(7) Whatever views may be held of the primary and secondary manifestations in syphilis, we believe that all tertiary and "parasyphilitic" manifestations are expressions of the reaction of hypersensitized tissues ("hyperallergie"). That is to say, during the previous stages of infection, the tissues have been so altered that they react more violently to a smaller dose of the spirochæte or its toxins.

Gummatosis is the reaction of hypersensitized connective tissues and blood-vessels, whilst "parasyphilis" is a hyperallergic reaction of the essential nerve-elements and neuroglia.

(8) The consequences of this hyperallergic reaction in the tissues of the central nervous system is death of any set of fibres or cells which happens to be attacked, and proliferative reaction on the part of the neuroglia within the same territory.

Thus, the clinical manifestations of "parasyphilis" are an expression of the reaction and necrosis of hypersensitized areas of the nervous system, evoked by reappearance of the *Spirochæta pallida*.

(9) This hypersensitive ("hyperallergic") state of the tissues of the central nervous system is produced, in all probability, by the passage of the spirochætes or their toxins up the nerves from the skin and mucous membranes during the secondary period. But it is also conceivable that it may be due to a slight "encephalitis" during this stage of infection.

The headache and lassitude, unaccompanied by any gross nervous lesions, which so frequently occur during the secondary stage, possibly represent clinically the period during which sensitization occurs.

(10) Thus, parasyphilis is a clinical conception which comprises the manifestations of a series of diseased states. From the pathological point of view, the term is inadmissible. These states depend on the reaction of hypersensitized tissues to the spirochæte or its toxins, and this reaction is as truly syphilitic as the production of gummata.

The difference between the consequences of the tertiary and of the "parasyphilitic" process lies in the nature of the tissues participating in the reaction. In the one case the connective tissue is capable of repair, and the focus is readily reached by the remedial agents. In the case of "parasyphilis," reaction of the essential nerve-elements leads to their death, and antisyphilitic remedies cannot readily reach the spirochæte.

REFERENCES.

[1] Altmann, Karl, und Dreyfus, G. L. *Münch. med. Wochenschr.*, 1913, S. 464, 531.
[2] Assmann, H. *Deutsche Zeitschr. f. Nervenheilk.*, 1910, Bd. xl, S. 131.
[3] Brosius. *Archiv f. Psychiat.*, 1903, Bd. xxxvii, S. 639.
[4] Dejerine, J. *Rev. de Méd.*, 1889, t. ix, pp. 81, 208.
[5] Ehrmann, S. *Deutsche med. Wochenschr.*, 1906, Bd. xxxii, S. 1115.
[6] Erb, W. *Neurol. Centralbl.*, 1892, Bd. xi, S. 161.
[7] *Idem.* *Deutsche Zeitschr. f. Nervenheilk.*, 1902, Bd. xxii, S. 100.
[8] Fournier, A. "Les Affections parasyphilitiques." Paris, 1894, p. 2.
[9] *Idem.* *Op. cit.*, p. 262.
[10] *Idem.* *Op. cit.*, p. 238.
[11] Fraenkel, Max. *Zeitschr. f. d. ges. Neurol. u. Psychiat.*, 1913, Bd. xi, S. 1.
[12] Hauptmann, A., und Hössli, H. *Münch. med. Wochenschr.*, 1910, Bd. lvii, S. 1581.
[13] Head, H. *Proc. Roy. Soc. Med.*, February, 1910, vol. iii (Neurol. Sect.), p. 49.
[14] Levaditi, C., et Roché, J. "La Syphilis," Paris, 1909, p. 285.

[15] McIntosh, J., and Fildes, P. "Syphilis," London, 1911, p. 220.
[16] *Idem.* *Zeitschr. f. Chemotherapie*, 1912, Bd. i, S. 79.
[17] Morel-Lavalée. *Gaz. des Hôpitaux*, 1892, t. lxv, p. 303.
[18] Mott, F. W. "System of Syphilis," London, 1910, vol. iv, p. 186.
[19] *Idem.* *Brit. Med. Journ.*, 1908, vol. i, pp. 10, *et seq.*
[20] Neisser, A. "Beiträge zur Pathologie und Therapie der Syphilis," Berlin, 1911, S. 200.
[21] Noguchi, H., and Moore, T. W. *Journ. of Exper. Med.*, 1913, vol. xvii, p. 232.
[22] Nonne, Max. "Syphilis und Nervensystem," Berlin, 1909, S. 418.
[23] *Idem.* *Op. cit.*, S. 284.
[24] *Idem.* *Op. cit.*, S. 402.
[25] *Idem.* *Op. cit.*, S. 174.
[26] *Idem.* *Op. cit.*, S. 175.
[27] *Idem.* *Deutsche Zeitschr. f. Nervenheilk.*, 1911, Bd. xlii, S. 214, *et seq.*
[28] Orr, D. *Rev. of Neurol. and Psychiat.*, 1903, vol. i, p. 639. Also several subsequent papers with Rows, R. G., *e.g.*, *Brain*, 1904, vol. xxvii, p. 460.
[29] Plaut, F. "Die Wassermannsche Serodiagnostik der Syphilis," Jena, 1909, S. 48.
[30] Plaut, F., Rehm, O., und Schottmüller, H. "Leitfaden zur Untersuchung der Zerebrospinalflüssigkeit," Jena, 1913, S. 28.
[31] *Idem.* *Op. cit.*, S. 136.
[32] Raymond, F. *Bull. et Mém. de la Soc. méd. des Hôp. de Paris*, Fév. 3, 1893, t. x, p. 55.
[33] Wassermann, A., und Plaut, F. *Deutsche med. Wochenschr.*, 1906, Bd. xxxii, S. 1769.
[34] Wilson, A. Read. *Brain*, 1912, vol. xxxv, p. 153.
[35] Wilson, S. A. Kinnier. *Proc. Roy. Soc. Med.*, 1908-09, vol. ii (Neurol. Sect.), p. 19.

THE BRAIN OF A MACROCEPHALIC EPILEPTIC.

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AND

GEORGE A. WATSON, M.B., C.M.

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PART I.—CLINICAL HISTORY.

THE subject of this communication was a male epileptic who was admitted into Rainhill Asylum under our care in August, 1901, and died there in January, 1910. He was a single man, by occupation a piano-tuner, and his age on admission was 28. His family history was good. His father was an intelligent man, a Nonconformist minister, and there was no record of insanity, epilepsy, or allied neuroses in the family. The patient himself had always enjoyed good health, and had never had any serious illness except an attack of pleurisy. He was bright and intelligent as a child, and early showed promise of great musical ability, but he was always of a nervous, excitable disposition. At the age of 9 years he seems to have had an attack of *petit mal*, but the first distinct fit occurred when he was 16, and since that time he remained subject to epileptic attacks at variable intervals. For about a year before admission, the parents of the patient had noticed a gradual mental deterioration, which doubtless had been coming on insensibly for some time previously, but no attack of active insanity occurred until ten days before admission, when he became delusional, excited and threatening, which necessitated his removal to the asylum. He was on admission a man of good physique, 5 ft. 10 in. in height, and 12 st. 10 lb. in weight, with all his viscera apparently healthy. The limbs were well formed and symmetrical; there were no deformities of any kind. The circumference of his head was 25 inches. His mental condition was one of partial dementia. He was dull and weak-minded generally, slow of speech with prolonged reaction time, but was nevertheless fairly intelligent, could give a good account of himself, and was a useful worker. His history thenceforward was that of epileptics generally. The frequency of his fits increased in spite of treatment by bromides, so that whereas in the year 1902 his fits had averaged 5·9 per month, these had increased in 1907 to 9 per month. Along with this went steadily increasing impairment of memory and intelligence; he also had periodical attacks of excitement, lasting for a few days at a time, during which he was violent and dangerous, such attacks usually leaving him on their subsidence somewhat duller than before. Even when at his best he was markedly irritable and quarrelsome and showed much emotional instability. The steady mental deterioration was well shown by the fact that when first admitted into the institution in 1901 he was a useful worker in the place, but by the end of 1906 he had become useless as such, and in 1909 he had not sufficient mind to employ himself in any way. Concurrently with this his health gradually failed, and he finally died of an attack of broncho-pneumonia at the age of 37.

AUTOPSY NOTES.

Autopsy twenty-two hours after death. Temperature of mortuary 40° F. Height 69½ in.; circumference of shoulders 35½ in.; of head 25½ in. No deformities. Skull markedly dolico-cephalic and symmetrical; density average; average frontal thickness 6 mm.: occipital 8 mm. Dura mater congested, of normal thickness. The superior longitudinal and lateral sinuses contained dark fluid blood. Sub-dural fluid clear and in slight excess. Pia-arachnoid very congested and somewhat œdematous but showed no abnormal opacity; it stripped from the hemispheres a little more readily than naturally in the frontal region and about naturally elsewhere.

The brain generally was rather soft in consistence and somewhat œdematous. There was slight general wasting of the prefrontal region of both cerebral hemispheres but little or no obvious wasting elsewhere, and there were no local surface softenings. The lateral ventricles were slightly dilated, with slight excess of clear fluid. Large granulations were present in the third ventricle, anterior part of the lateral ventricles and in the lateral angles of the fourth ventricle. The main cerebral arteries were normal in distribution and appearance; veins congested.

The bodily organs generally were congested but showed no features of interest. The internal secretory organs all appeared to be normal. Areas of broncho-pneumonia were present in both lower lobes and a few patches of early atheroma in the thoracic and abdominal aorta, mostly in the latter. There were no signs of syphilis.

Weights of organs in grammes: Right lung 730; left lung 700; heart 235; liver 1,100; spleen 125; right kidney 155; left kidney 155.

The weight of the encephalon, immediately after removal from the body:—

Total weight, unstripped of membranes		2,130 grm.
Right hemisphere unstripped ...	947 grm.; stripped	918 grm.
Left ,, ,, ...	924 grm.; ,,	900 grm.
Cerebellum, pons and medulla, unstripped		228 grm.

The encephalon in this instance is thus 730 grm. above the average weight of the unstripped male encephalon, viz., 1,400 grm., as given by Marchand [14]. It may be calculated from Marchand's figures that 609 grm. is the average normal weight of each unstripped cerebral hemisphere. In this specimen this weight is exceeded by 338 and 315 grm. in the right and left hemispheres respectively.

The difference in weight of 23 grm. between the right and left hemispheres can scarcely be looked upon as unusual in view of the large size of the hemispheres, nor can the loss of 29 and 24 grm. occasioned by stripping the right and left hemispheres respectively, as 20 grm. is approximately the amount which the normal hemispheres lose in weight on stripping.

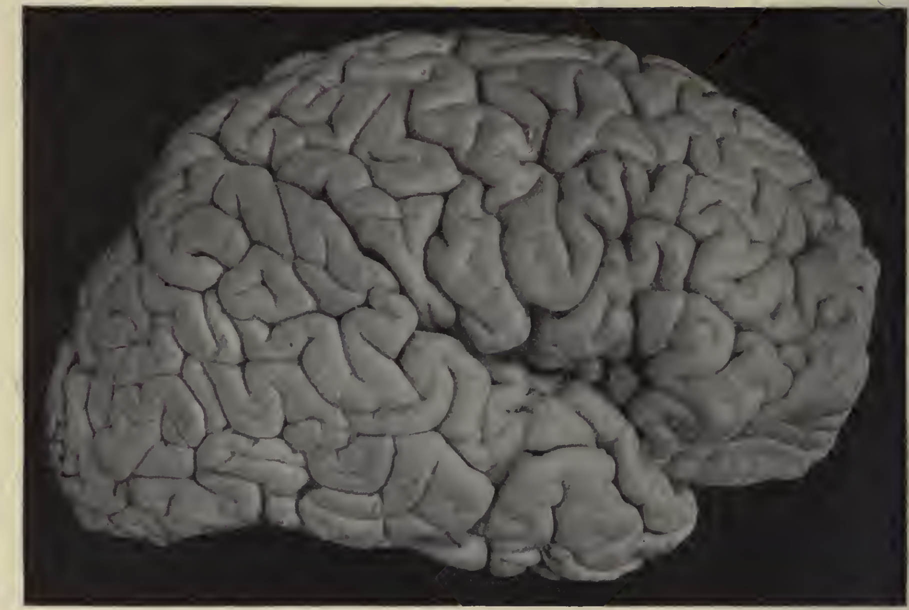

FIG. 1.

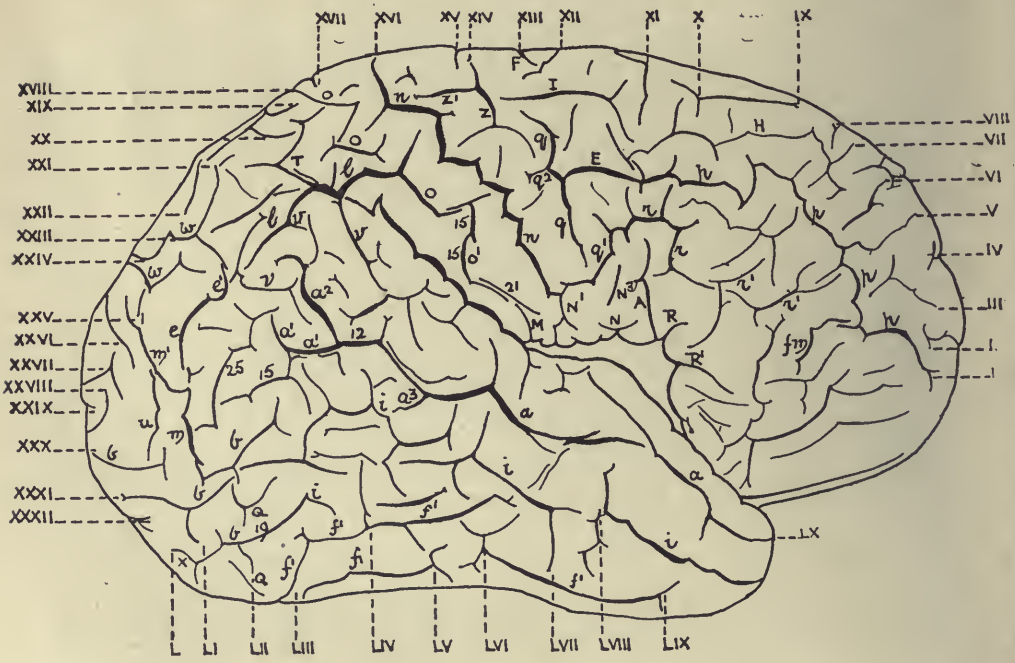

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FIG. 1*a*.

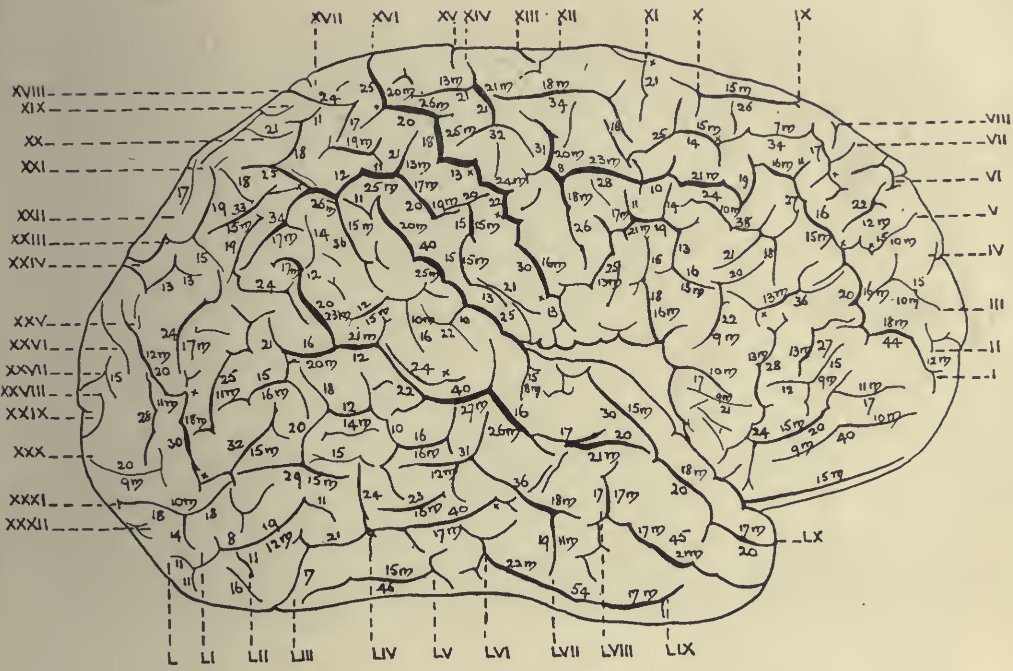
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Fig. 1*b*.

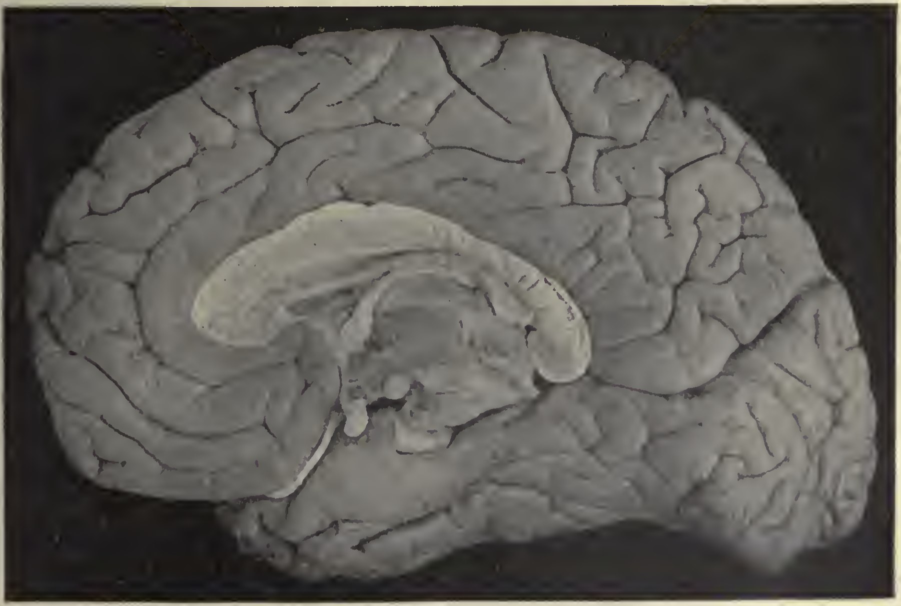

Fig. 2.

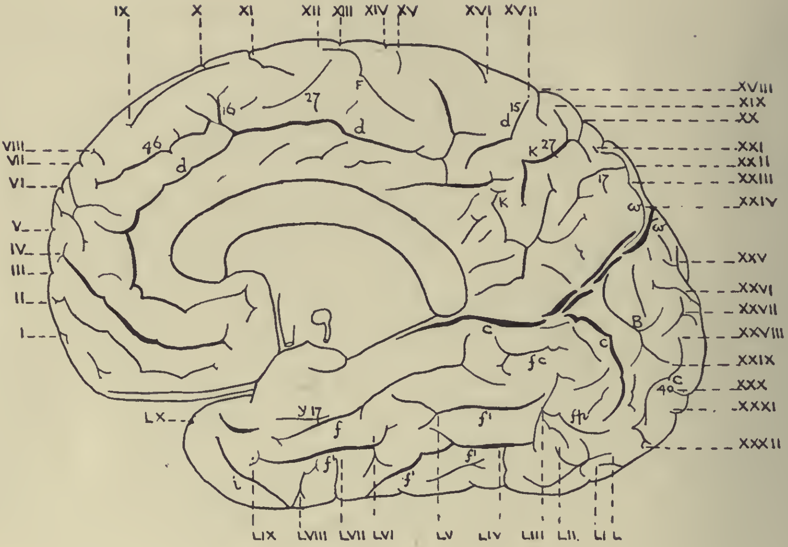
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FIG. 2*a*.

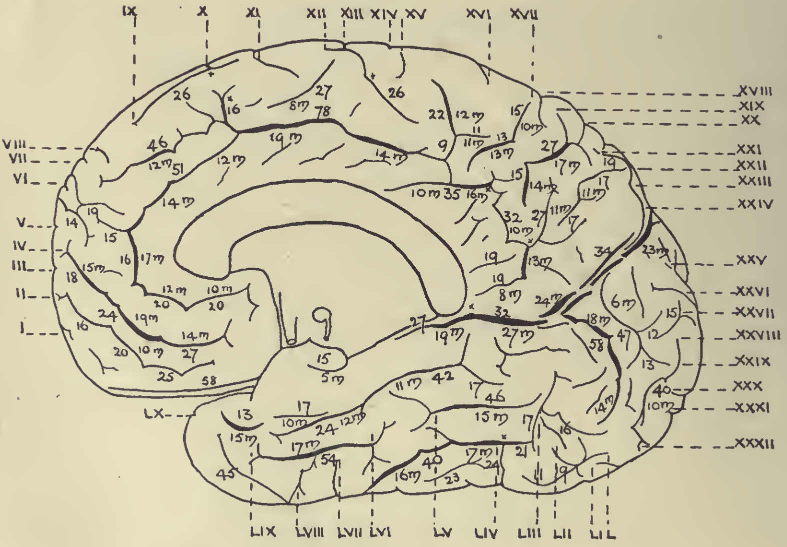
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FIG. 2*b*.

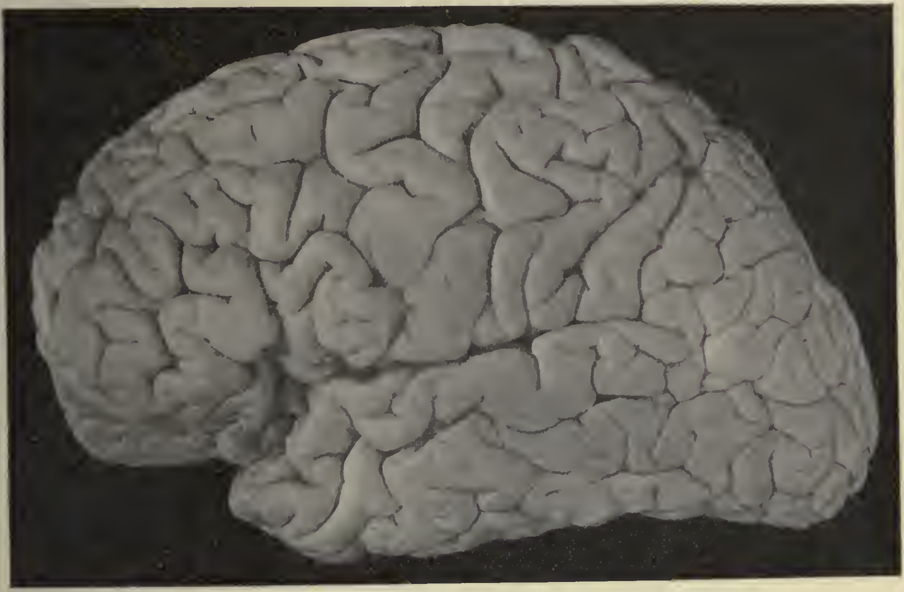

FIG. 3.

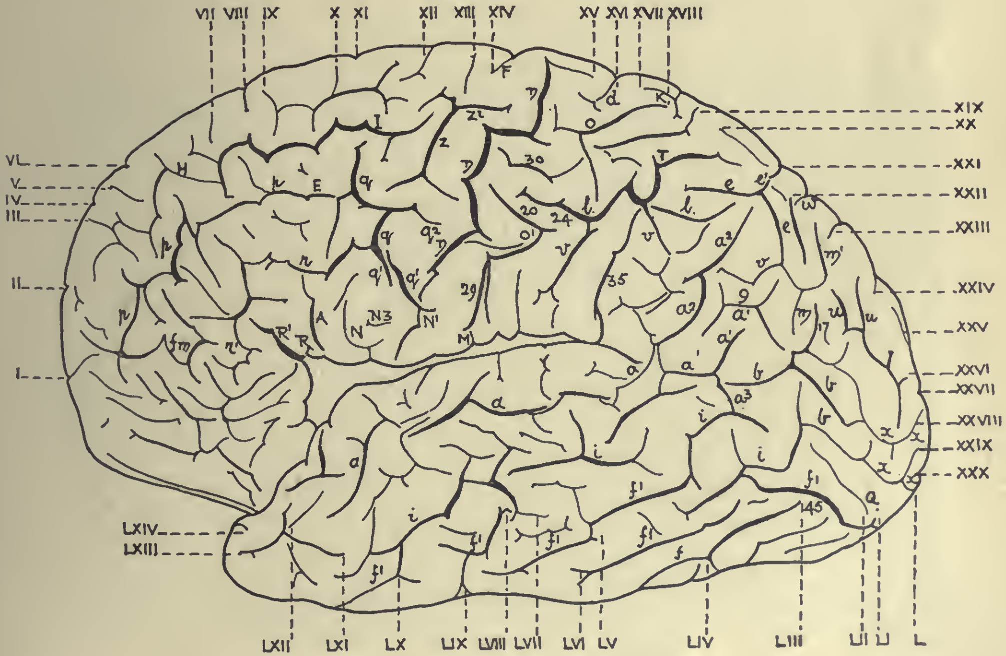
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FIG. 3*a*.

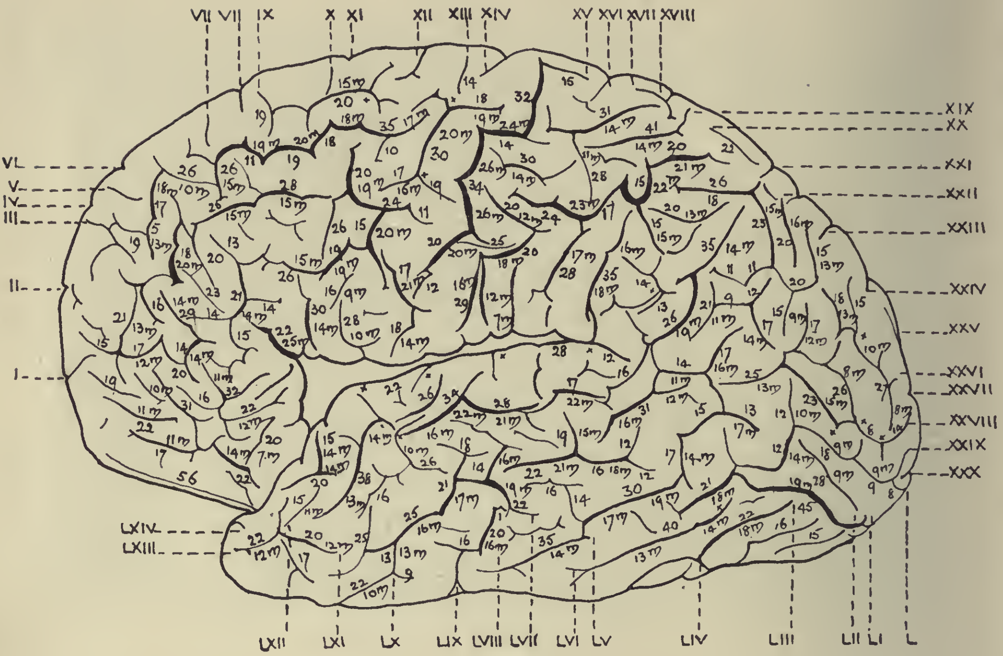
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FIG. 3b.

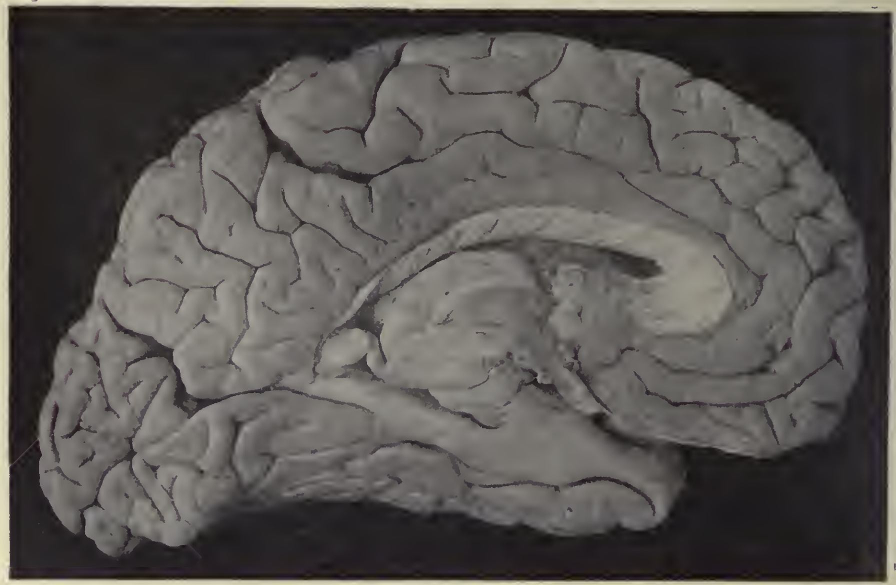

FIG. 4.

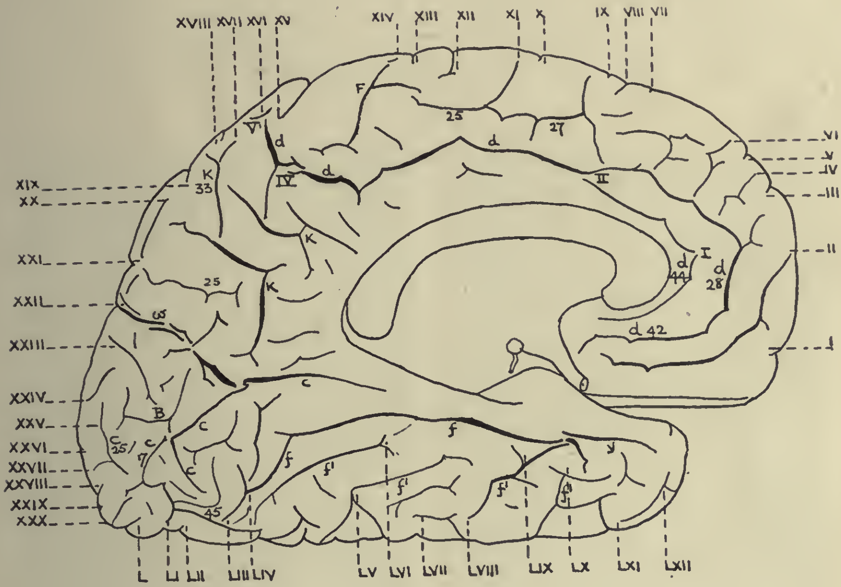
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FIG. 4*a*.

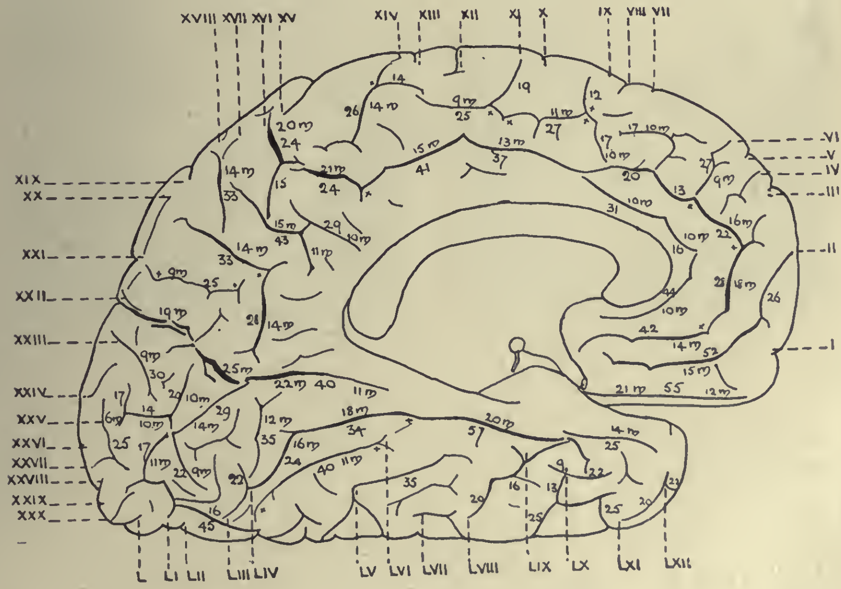
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FIG. 4*b*.

The normal ratio of the conjoined cerebellum, pons, and medulla to the cerebrum is given by Huschka as 13 : 87. In this specimen, the ratio being 10·6 : 87, the weight of the cerebrum relatively to that of the conjoined cerebellum, pons, and medulla is in excess of the normal.

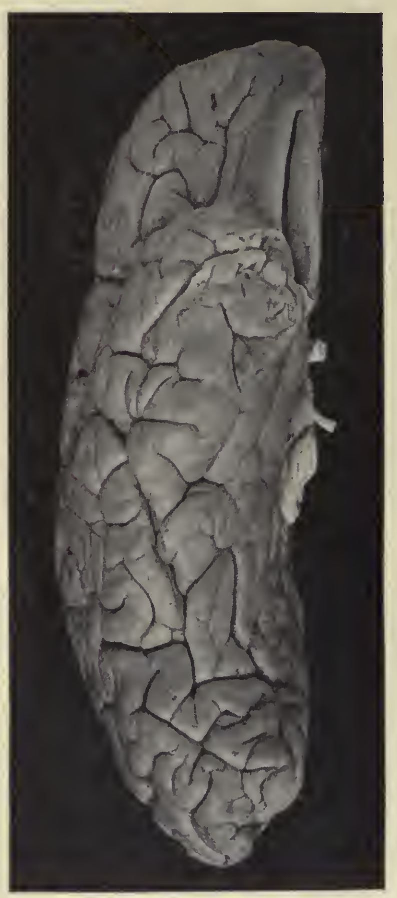

FIG. 5.

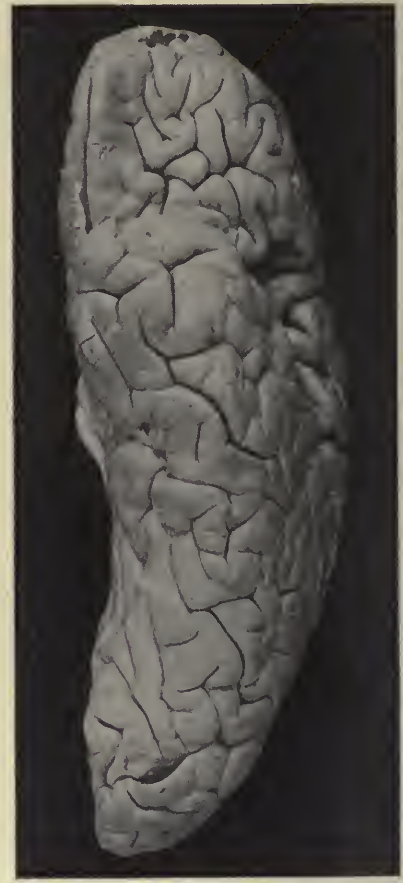

FIG. 6.

Looked at *generally* the cerebral hemispheres are unusually long as compared with their breadth. The different parts, however, appear to be in about normal proportion, excepting that the fronto-polar region on each side strikes one as being decidedly broad, relatively as well as absolutely, the superior portion of each third frontal gyrus is somewhat defective, and occipital lobes are relatively somewhat small.

The cerebellum, pons, and medulla appear as regards their shape and constitution to be in every way normally developed, and these parts are well covered by the cerebrum.

The encephalon is one of the largest—uncomplicated by any gross pathological change—of which there is any authentic record.[1] It is of interest to note that in several instances which have been reported of extraordinarily heavy brains the possessors have suffered from epilepsy.

The encephalon in this case much exceeds in weight that of the great majority of the 108 eminent men whose brain weights have been collected by E. A. Spitka [18], the nearest approach to it, in regard to weight, viz., 2,012 grm., being that of Turgenev, the Russian poet and novelist. The cerebral hemispheres are also, on the whole, about the most generally complex in pattern which we have hitherto seen. So far as can be judged from the drawings they are more complex than are those of any of the eminent men illustrated in Spitka's work, either those specially described by himself or by Retzius and others.

THE DRAWINGS OF THE CEREBRAL HEMISPHERES.

As illustrations supplementary to the photographs, drawings have been prepared something after the manner of Kohlbrugge [12] and [13] and of Cole [8]. These are freehand drawings based upon tracings of the photographs of the hemisphere. In the case of the lateral surface a considerable extension has been made towards the boundaries of the tracing so as to obtain in a single picture complete, or almost complete, views of the orbital surface, and of the fronto-polar and occipito-polar regions, as well as of the dorsal aspect of the hemisphere. The mesial aspect is shown in a similar manner, but as so much more of this surface, as compared with the outer, is almost flat a much less extension towards the boundaries of the drawing has been necessary. The drawings are thus, as Cole states with reference to his own, " a sort of Mercator's projection, though, of course, not mathematically exact. . . . The longitudinal dimensions of the parts about the crest of the hemisphere are unavoidably exaggerated . . . but their transverse dimensions, radial in the drawing, are given as nearly as possible in their true proportion."

---

[1] We have been able to find records of three human brains only, whether accompanied by pathological changes or not, of greater weight than the one under consideration, although it is possible that there are others which have escaped our search. These three are as follows :—

(1) Van Walsem's [22] case—2,850 grm.

(2) Sims' [17] case—2,400 grm. (Quoted by Anton [1] and Kohlbrugge [12].)

(3) A case mentioned by Hermann Pfister [16] 2,222 grm. There are reasons, however, for believing that there were gross pathological changes in this case.

The drawings differ from those of Kohlbrugge and Cole in that an attempt has been made to give an adequate display of the sulci and gyri of the under surface of each hemisphere by making a considerable extension in this direction of the drawings of the lateral and mesial aspects. The position of borders, such as the superciliary and occipito-temporal, can be seen on comparison with the photographs.

The drawings are in three sets. In one set (figs. 1*b*, 2*b*, 3*b*, 4*b*), the Arabic numerals *without* the letter *m* adjacent to them show the estimated length in millimetres of the different sulci, or portions of these, against which they are placed. A small + is put against a point from which a portion of a sulcus was measured to its extremity or from point to point along the sulcus. These measurements thus do not convey the idea of length from point to point, but from them may be gathered the estimated length of a sulcus. The extent to which the drawings are necessarily inexact in certain places can be seen from these measurements.

The drawings give a more accurate idea of the composition of the sulci than do the photographs; annectants are usually more clearly indicated, and the representation of mere vascular grooves, which may appear as shallow sulci in the photographs, is omitted from the drawings.

The Arabic numerals *with* the letter *m* adjacent to them indicate the estimated depth, in millimetres, of the several sulci at about the points against which the numerals are placed. Owing to obvious difficulties, however, all these measurements can only be regarded as approximately correct, and are merely of relative value.

The Roman numerals have been employed after the manner of Kohlbrugge and of Cole (the former uses Arabic numerals for this purpose) as marks by which one may identify corresponding points in two views of the same hemisphere. For facility of reference in these very complex hemispheres a considerable number of these points have been indicated. Many of the sulci, or portions of these, appearing in different views of the same hemisphere may also be identified by the Arabic numerals placed against them.

In another set of drawings, viz., figs. 1*a*, 2*a*, 3*a*, 4*a*, the sulci, the identification of which is certain, or fairly certain, have letters placed against them corresponding to the letters used by Kohlbrugge in his drawings. For the sake of clearness all the numerals referring to measurements have been omitted in this set of drawings excepting certain Arabic numerals, similar to those employed in the first set of drawings, which have been placed against certain sulci referred to in the text, the identification of which is doubtful, or to which special attention is directed.

The third set of drawings, figs. 7 and 8, will be referred to under Part II.

METHOD OF HARDENING THE CEREBRAL HEMISPHERES.

The cerebral hemispheres were hardened in 5 per cent. formalin after being stripped of their membranes, each hemisphere being laid on its mesial surface supported by wool. This method was adopted because it was originally intended to attempt micrometric measurement of sections from various regions of the cortex, and in order to obtain results comparative with other control cases it was considered advisable to strip the cerebrum in the fresh state. Unfortunately, although the tissue was fairly satisfactory for ordinary microscopical examination, it was found to be unsuitable for micrometric measurement.

MEASUREMENTS OF THE CEREBRAL HEMISPHERES.

These are in three sets. The second and third sets, particularly, have been made according to E. A. Spitka's [18] system. This author states that those measurements are best which can be reduced from absolute to relative values wherein some unit of length, preferably the maximum cerebral length, is used as a basis of expression rather than so many inches or centimetres. Hence centesimals of the length of the cerebrum are used, so that all brains may be compared, "no matter what their size or what the degree of shrinkage may be, so long as there is no actual distortion."

The method of hardening above described unavoidably leads to a certain amount of distortion of the hemispheres. Consequently it is doubtful if the measurements of these given below are of much value, partly for this reason and partly because of the difficulty of finding fixed points. In fact some writers advocate the abandonment altogether of any attempt at such measurements, believing that they are not only worthless but actually misleading. It is possible, however, that such measurements would be of some interest and value if compared with corresponding ones made upon hemispheres hardened in a similar manner, and which were originally not markedly atrophied or soft and flabby.

Measurements of the Cerebral Hemispheres.

Compared with the average measurements, when obtainable, of the brains of ten ordinary and normal individuals (Spitka [18]). All the measurements are given in millimetres.

I.—Principal diameters, &c.

	Right hemisphere	Left hemisphere	Average when obtainable
Maximum length	216	223	172
Maximum width	65	59	—
Maximum width of cerebrum 124	—	—	139
Cerebral index $\left\{\dfrac{\text{Breadth} \times 100}{\text{Length}}\right.$ .. 55·6	—	—	81
Maximum depth	140	136	—
Mesial length	382	380	—
Lateral length	270	275	—
Callosal length	103	113	—
Precallosal length	42	38	—
Postcallosal length	81	82	—
Occipito-temporal length	172	173	—
Sylvian angle	45°	28°	—
Rolandic angle	66°	64°	—

II.—Arc measurements, along the dorsi-mesial border.

	Right hemisphere	Left hemisphere	Average when obtainable R.	L.
Frontal arc	235	237	155	155
Parietal arc	79	79	55	57
Occipital arc	80	85	59	57
Cerebral indices (expressed in centesimals of the total fronto-occipital marginal arc)—				
Frontal index	59·6	59·1	57·7	57·7
Parietal index	20·1	19·7	20·4	21
Occipital index	20·1	21·2	22·1	21·3

III.—Horizontal distances (expressed in centesimals of the hemicerebral length).

From cephalic point to—

		Right hemisphere	Left hemisphere	Average when obtainable R.	L.
Lateral aspect	(1) Tip of temporal lobe ..	20·3	22·4	23	24
	(2) Sylvian - presylvian junction	28·7	32·2	30	30·4
	(3) Ventral end of central fissure	40·7	40·8	42·2	44·4
	(4) Sylvian - episylvian junction	55·1	51·5	55·9	60·5
	(5) Caudal point	—	—	100	
Mesial aspect	(6) Frontal edge of callosum ..	19	16·5	—	22
	(7) Porta (foramen of Monro)	34·2	36	—	41·2
	(8) Dorsal end of central fissure	69	67·6	—	63·9
	(9) Dorsal intersection of paracentral fissure	74	70·2	—	68·2
	(10) Caudal edge of callosum ..	65·7	66·2	—	64·2
	(11) Occipito-calcarine junction..	79·6	79·5	—	74·7
	(12) Dorsal intersection of occipital fissure	92·5	90·3	—	86·2

Whatever view may be taken of the value of these measurements, a brief allusion may be made to one or two points revealed by them.

The length of the hemispheres as compared with their breadth is very great, so that the cerebral index, viz., 55·6, is remarkably low. This cannot be wholly accounted for by the method of hardening adopted, i.e., by a tendency for the hemisphere to spread out flat and thin when lying on its mesial surface. It is almost certain that the latter method has some influence in reducing the cerebral index, particularly in the case of brains which show much wasting and dilatation of the lateral ventricles. Yet the cerebral index in this specimen, which was little wasted, is decidedly smaller than is that of any of the other brains in our possession which were hardened in a similar manner, and which were measured for comparison, in spite of the fact that many of these control brains were much atrophied.

The measurements (6, series III) would suggest that the mesial part of the frontal lobe in front of the corpus callosum is relatively rather small, especially in the left hemisphere, but the remainder of the frontal lobe is in almost normal proportion.

The occipital index apparently shows that the occipital lobe is relatively rather small, especially on the left side.

Other departures from the average in the measurements may perhaps be accounted for, or at least partly so, by a certain amount of distortion of the hemispheres.

General Account of the Cerebral Hemispheres.

In view of the clearness and sufficient accuracy with which the course and dimensions of the sulci are represented in the drawings, no systematic description of these or of the gyri appears to be necessary. The following general account will serve to direct attention to the main features shown by the convolutional pattern of the hemispheres. The identification of the sulci has been in some instances a matter of considerable difficulty, and we are much indebted to Dr. S. J. Cole for valuable help in this connection. Dr. Kohlbrugge has also kindly revised the lettering of the sulci. We are ourselves, however, entirely responsible for all the opinions expressed.

In addition to comparison with the descriptions and drawings of the sulcal pattern of the numerous cerebral hemispheres given by Kohlbrugge [12] and [13], indications of departure from the usual and normal brain pattern, such as are regarded of importance by many other observers, have been carefully looked for. These have been summarized by Mickle [15] as occurring in the following directions: (1) In superiority, indicating active development and high evolutionary grade. (2) In aberrant irregularity and bizarre arrangement of the sulci and gyri, which is taken to signify formative activity, or over-activity but ill-directed. (3) In inferiority by defect: (*a*) either as a developmental defect, so that there is persistence, more or less, of fœtal characters in place of advance to adult form; (*b*) or as an evolutionary reversion to brain types of lower races of mankind, or to lower animal types.

THE SULCI AND GYRI OF THE CEREBRAL HEMISPHERES.

We will deal with the interlobar fissures first, and then with the sulci and gyri of the several lobes.

The Interlobar Fissures.

The fissure of Sylvius.—The general course of this fissure is more steeply inclined on the right side than on the left, but this is usually regarded as a normal difference between the two hemispheres both in man and in most of the apes; the macaque, according to Cunningham [9], showing an exception in this respect.

The main portion of the posterior limb of the fissure is, as is usual, considerably longer on the left side than on the right. The posterior limb ends on both sides in a shorter descending and a longer ascending ramus. It seems doubtful how much of the latter really belongs to the Sylvian system. It is broken by several deep interdigitations, and just above the mark 35 in the left hemisphere, and at a corresponding place in the right is a deep gyrus. Probably only the lower piece of the apparent ramus, below the deep gyrus, belongs to the Sylvian; the upper piece being a subsidiary sulcus of the inferior parietal lobule, although it does not actually join the sulcus interparietalis.

In the right hemisphere the anterior limb possesses two rami, a posterior one, R, which is short and deep—the apparent sulcus seen in the photograph joining this is merely a vascular groove—and an anterior one, R^1, having a forward and downward direction. On the left side the anterior limb shows only one well-formed ramus, R^1, the sulcus behind this, R, representing the ascending ramus, being quite small. Further reference to these rami is made on p. 51.

The sulcus centralis, n. N^1.—This sulcus follows a fairly usual course on both sides, excepting that in the right hemisphere it is straighter than is common, and the typical backward extension of its upper extremity is absent. Each sulcus shows several deep annectants, and the upper and lower buttresses of Symington and Crymble [19] are rather more distinct on the right side than on the left.

The small sulcus, lettered N^1, when in the position it occupies in these hemispheres, should probably be regarded as part of the s. centralis, for we have found in several cases that a similar sulcus forms a posterior limit to the Betz-cell area. The sulcus in question is on the left side, separated from the *n* sulcus by a narrow superficial bridge—the lower bridge of Mickle [15]. The presence of such a bridge, if broad, would probably be a mark of inferiority.

Superficial union of the right s. centralis with the s. precentralis, and with the Sylvian, by means of an intermediary sulcus (N^1) may also be noticed. This union, when present, is regarded by Mickle as aberrant.

A short, straight, smooth-walled s. centralis shallow relatively to the s. interparietalis resembles that of lower apes, and it has been asserted that in poorly-developed brains and in those of negroes the s. centralis is less sinuous than normal. But Mickle [15] states that this condition is not often a criterion of low type, for some decidedly inferior brains have sinuous or zigzag central fissures. In this case the right s. centralis, although rather straighter than usual, is of relatively good length, is of good depth, and possesses well-marked deep annectants.

The fossa parieto-occipitalis, w.—This is well closed on both sides. The sulci composing the complex, as seen on opening up the fossa, are somewhat diagrammatically shown in the drawings, for all the internal annectants are deeply placed. On the right side the dorsal elements forming the incisura are two in number (*w*, *w*) and the anterior of these especially is of considerable length. On the left side there is only one dorsal element, and this is short. The cuneo-limbic and cuneo-precuneal annectants are deep, and are very similarly disposed on the two sides.

The sulcus calcarinus, c. Right hemisphere.—The anterior portion or stem passes forwards for a somewhat unusual distance anterior to the splenium of the corpus callosum. The posterior portion curves markedly downwards and backwards in the main part of its course, its lower end bending slightly forwards. It is separated posteriorly by a broad superficial posterior cuneo-lingual annectant from an undulating sulcus (marked *c* 40), which also probably forms part of the calcarine system. The anterior cuneo-lingual annectant is somewhat small, and is for the most part deeply placed. Three small deep interdigitations are seen along the course of the posterior calcarine proper.

Left hemisphere.—The stem of the sulcus follows a usual course. The posterior division passes at first downwards and backwards, and then makes a sudden bend downwards and slightly forwards—the general direction of this portion of the sulcus being very similar to that on the right side. The small sulci behind (marked *c* 17 and *c* 25) probably also belong to the calcarine system. The anterior cuneolingual annectant is small and deeply placed, the posterior is superficial and narrow.

In both hemispheres the stem of the sulcus shows the normal obliquely downward cut into the brain substance, whilst the posterior portion, as is usual, incises the cerebrum at about right angles to the surface.

On the right side the posterior calcarine proper ends rather further forwards than is common in the well-developed human brain. This, together with the presence of the curving shallow sulcus behind, separated by a broad superficial annectant, may possibly be some indication of a phylogenetic reversion.

In the left hemisphere the irregular arrangement of the posterior calcarine and of the separate terminal pieces behind this is atypical, and perhaps may be regarded as a sign of aberrancy and inferiority.

The sulcus collateralis, f, fc; and *sulcus rhinalis, y.*—The right s. collateralis must probably be regarded as being defectively developed. It is in two pieces separated by a broad superficial annectant. Both portions of the sulcus are unusually shallow and are smooth walled. The sulcus marked *y* 17 represents a s. rhinalis; between this and the main portion of sulcus *f* is a narrow superficial gyrus rhinencephalo-temporalis posterior. There is in this hemisphere a short incisura temporalis.

The left s. collateralis is better developed than is the corresponding sulcus of the right side. It has a fairly usual course: is of good depth and shows three deep interdigitations in its posterior portion. The sulcus marked *y* represents a s. rhinalis and there is a fairly broad gyrus rhinencephalo-temporalis posterior, for the most part deeply placed, and a narrow gyrus rhinencephalo-fusiformis. No distinct incisura temporalis is seen in this hemisphere. The sulcus rhinalis on both sides probably forms a partial boundary to Brodmann's area of cortex No. 28.

The sulcus cinguli, d. Right hemisphere.—The pars anterior and pars intermedia are typically placed. No definite Brücke of Eberstaller is seen along the course of these portions of the sulcus, although several small deep interdigitations are present. The pars posterior (*d* 15) is separated from the pars intermedia by a broad superficial annectant representing either Brücke III or IV whilst a Brücke V (the gyrus arcuatus anterior of Retzius), arches round the upper end of the pars posterior. The pars intermedia forms a definite junction with the sulcus subparietalis (K) (see fig. 2*b*). Such a union is shown in some of the drawings by Kohlbrugge [12] and [13] of Malayan and Javan brains. It is looked upon by Mickle [15] as aberrant in the human brain and as pointing to a phylogenetic reversion, although probably a junction of the *K* sulcus with the pars posterior of the sulcus cinguli would be of greater significance in this respect.

Left hemisphere.—The anterior reaches of the sulcus in this hemisphere must probably be looked upon as being duplicated, the sulcus marked *d* 28, 42 forming a s. cinguli superior. But below and behind this, and having a somewhat similar direction in relation to the genu of the corpus callosum, is another but much shallower sulcus (*d* 44) which may be regarded as part of the sulcus cinguli. There are several deep interdigitations, but no definite Brücke occurs along the course of the pars intermedia and sulcus *d* 28, 42. But the lower and posterior sulcus, *d* 44, has an almost superficial annectant crossing it at the mark I, and it is separated from the pars intermedia by a surface annectant at the mark II. If this sulcus, *d* 44, be regarded as part of the s. cinguli then these annectants have the usual position of Eberstaller's Brücke I and Brücke II respectively. The pars posterior is in two divisions—horizontal and ascending—separated from each other by a Brücke IV. A Brücke V is also present.

Duplication of the forepart of the s. cinguli appears to be commoner in the left hemisphere than in the right (Mickle [15] and Kohlbrugge [12] and [13]), and, when present, may be regarded as a normal difference between the two hemispheres.

Mickle [15] states that it is not infrequently difficult to appraise correctly the significance of certain appearances of the sulci. "Like words in a sentence, their meaning varies with the context." Duplication or triplication of the sulcus cinguli may be taken as a case in point. This may sometimes mean the abnormal persistence in the adult of a fœtal character, and at other times aberrant formative activity, but such interpretations can probably only be placed upon the appearance if accompanying conditions show a defective, reverting or aberrant tendency. If these conditions evince a normal or high brain type, the duplication of the sulcus in question may probably be deemed to manifest fissure wealth.

The Frontal Lobes.

The external Surface.—The *precentral* system of sulci (F, *z*, *zi*—q, q^2,q^1) is well developed and is for the most part typical on both sides. The sulcus F, placed rather far forward in the right hemisphere, is a good example of the solco inflesso of Lussana, or inflected fissure of E. A. Spitka [18] or s. præcentralis mesialis. The ramus sagittalis posterior (*zi*) of the s. præcentralis superior is well developed in both hemispheres.

The *s. frontalis superior* (I and H) is comparatively simple and shallow in the right hemisphere as compared with the left, probably in association with the especially good development of the mid-frontal system in the former hemisphere.

The *s. frontalis mesialis* is fairly well developed on both sides, rather better on the left than on the right.

The sulci q and q^2 represent the *s. præcentralis medius* of some authors. The ramus horizontalis anterior of Eberstaller forms an important branch of this sulcus.

The *p* system of sulci (in part the *s. frontalis medius*) is unusually well developed on both sides. In the right hemisphere the anterior portions of this system form a typical *s. fronto-marginalis*, consisting of a stem and a mesial branch. There is also a lateral branch (*fm*), separated from the stem by an annectant, but the mesial branch in this instance, as is commonly but not invariably the case, is obviously the direct continuation of the main stem. The stem and mesial branch well represent a sulcus identified by Bolk [3] with the *s. rectus* of lower apes.

On the left side the arrangement is not quite so typical. The stem divides into a shorter mesial and a longer lateral branch, and it is not clear which of these two is the direct continuation of the main stem.

The sulcus q^1—in part the *s. præcentralis inferior*—appears to be duplicated in the left hemisphere. The posterior of the two sulci superficially joins the N^1 sulcus, but a deep gyrus crosses the sulcus almost opposite the lower end of the *n* sulcus. On the right side the q^1 sulcus is single but is somewhat unusual. It appears to be a lower portion of the s. præcentralis inferior forming an aberrant though shallow connection with the *n* sulcus and with the Sylvian fossa by means of an intermediary sulcus N^1.

The *inferior frontal* system of sulci r, r^1 is fairly typical in both hemispheres, but on the right side the different elements of the system are separate from each other, whilst on the left side they are joined.

The *subfrontal* region—using the term subfrontal according to Brodmann's [6] meaning—is on the whole comparatively small and simply convoluted. The orbital (or inferior) operculum is well developed on both sides. On the right side the anterior limb of the fissure of Sylvius possesses two definite rami, R, R^1, enclosing between them a relatively moderate sized intermediate (or triangular) operculum. In the left hemisphere this operculum is decidedly small, as there is only one well formed anterior limb of the Sylvian complex. The latter arrangement is probably more common on the right side than on the left. The superior operculum is somewhat defective, especially in the right hemisphere. The amount of exposure of the insula as seen in the photographs and drawings is no doubt exaggerated owing to the membranes having been stripped from the hemispheres before hardening. This would probably affect the position of the temporal more than that of the frontal opercula, and owing to a certain defect of the intermediate and superior frontal opercula it is probable that in the natural state there was some undue exposure of the insula.

A *sulcus diagonalis* is not easy to identify with certainty in these hemispheres. As Kohlbrugge [12] and [13] has suggested (and Bolk [3] agrees), a true s. diagonalis is part of the s. præcentralis inferior which has become detached owing to the rising up of a gyrus in the depths of the latter sulcus. The sulcus lettered A in both hemispheres in this specimen may probably be regarded as a s. diagonalis owing to its position in front of the sulcus identified as the s. subcentralis anterior (N), and owing to the close proximity of its lower end to the anterior Sylvian ramus.

A remark may here be made concerning the *sulcus arcuatus*. Cole [8] believes that the upper or horizontal limb of the arcuate sulcus of lower apes is often represented in the human brain by a part of the s. frontalis superior. According to this view the course of the s. arcuatus would probably be represented in this specimen on the right side by the sulci lettered q^1, the lower part of q and H, and on the left side by those marked q, q and I.

The mesial surface. The marginal gyri and paracentral lobules.—This surface is comparatively simply convoluted in the right hemisphere. In the left fairly-well developed branches marked 25, 27, constituting the *mesio-frontal intragyral sulcus* of Mickle [15] or *fissure fronto-marginalis* of Spitka[1] [18], divide part of the marginal gyrus into two tiers. This sulcus on the right side is represented by the shallow furrow marked 27, and possibly also by the furrow marked 46 which makes a shallow connection posteriorly with the branch of sulcus *d* marked 16. The sulcus appears often to be better developed in the left hemisphere than in the right in common with the more frequent duplication in the former hemisphere of the anterior reaches of the s. cinguli.

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[1] *Sulcus gyri marginalis* would probably be a more appropriate name for this sulcus than fissura fronto-marginalis, in order to avoid confusion with the sulcus fronto-marginalis.

The sulcus L of Kohlbrugge (*cephalic paracentral* of Wilder, *s. paracentralis* vel *præparacentralis*) is not present in the left hemisphere, and the branch of sulcus *d* marked 16 in the right is probably placed too far forward to represent the sulcus. Kohlbrugge regards the sulcus L as of little importance.

The *rostral* sulci are long, simple and typically placed in the right hemisphere, but in the left, if the sulcus, *d* 28, 42 is to be looked upon as a s. cinguli superior, only one rostral sulcus is present.

The left paracentral lobule is smaller than the right and is smooth. On the right side the lobule is scored by a long branched upturn of the s. cinguli.

The orbital surface.—There is some tendency to keeling of this surface in both hemispheres. The orbital sulcus shows the usual transverse and sagittal elements. The transverse element is of great length on the right side, and its outer end passes over the superciliary border for a considerable distance. The whole system, however, is much more complex in the left hemisphere than in the right, the sagittal elements being more numerous and more branched than is common in the former hemisphere, and they tend to almost completely insulate portions of the brain substance.

Remarks on the Frontal Lobes.

(1) The general size of these lobes is about normally proportionate to that of the remainder of the hemispheres. Each hemisphere, however, is distinguished by the great breadth and complexity of its fronto-polar region in contrast to the condition of the subfrontal region which on both sides is partially defective and is relatively simple in pattern. There is now much evidence, to mention only that brought forward by Flechsig [11], Bolton [4] and [5], and Brodmann [6], to show that the latest regions of the frontal lobe to develop, both ontogenetically and phylogenetically, are the subfrontal and prefrontal.[1] In the cerebral hemispheres of the insane it is common to find one or other,

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[1] *i.e.*, the prefontal in the meaning of Bolton and not in that of Brodmann.

or both, of these regions especially affected, either as a congenital defect, or as the result of loss due to cerebral wasting. In this particular specimen it is therefore of interest to note that whilst the prefrontal region is of great breath and is complex in pattern, the subfrontal is relatively defective and comparatively simply convoluted.

(2) The main sulci are for the most part deep, much curved, and possess many secondary spurs. The development of the sulci has proceeded on fairly regular lines and, as we consider, in the direction of superiority. The only definite tendency to insulation of portions of the cortex has occurred in the right orbital region. This tendency to the formation of islands of cortex either by branching and re-uniting of primary sulci or owing to the presence of unusual sulci, is looked upon by Mickle [15] as a sign of aberrant formative activity. As regards the external surface of the frontal lobes the left hemisphere appears to be slightly more complex in pattern than the right, although in places the latter is a little better convoluted than its fellow. With respect to the mesial and orbital surfaces of the lobes, the left side is decidedly superior to the right in convolutional complexity.

(3) The good development of the external sagittally coursing sulci, especially of the sulcus frontalis medius, which on the left side in this specimen is remarkably well formed for a *left* hemisphere, divides this part of each frontal lobe into four distinct, and for the most part, broad gyri. The superior of these is still further partially subdivided by branches of the sulcus frontalis mesialis which is also rather better developed on the left side than on the right.

According to Kohlbrugge [13] this four tier type of external frontal conformation is the common arrangement for the brains of Australians. Mickle [15] states that, found in some criminals, lunatics and mental defectives, it has been said to indicate marked aberrancy, Benedikt indeed believing that it is a sign of grave reversion to the four tier type of certain lower animals. Mickle himself, however, argues that, at least in many instances, this four (and five) tier type marks a higher than usual and not a lower brain formation, especially when due to division of the first frontal gyrus by unusual development of the s. frontalis mesialis. The same applies, although less convincingly, to the four tier form produced by marked development of the s. frontalis medius. The author quoted believes, contrary to Benedikt, that the latter is the more common arrangement, and this is in agreement with our own experience. The type thus formed has not infrequently been seen in the larger cerebral hemispheres obtained at the Rainhill Asylum, and these hemispheres have, as a rule, belonged to people of originally good intelligence. Mickle, after concluding that instead of degradation and reversion, the four tier form must indicate in many cases a rather high position in brain evolution, remarks that, "this is indeed compatible with mental aberrancy, with unstable and labile mental activities, lively and powerful but not well directed—in a word, a brain function lacking in balance."

The Parietal Lobes.

The external surface.—The sulcus lettered M forms a fairly typical *s. subcentralis posterior* in both hemispheres.

The *sulcus post-centralis.* On the right side a series of sulci (*o*, o^1) make an almost complete boundary to the post-central gyrus, the annectants passing between this gyrus and the parietal lobules being narrow and mostly rather deep. In the left hemisphere the several elements of the post-central sulcus are for the most part widely separated from each other by broad superficial annectants. The superior branch (*o*) in this hemisphere shows the common arrangement of a stem bifurcating at its upper end to embrace the extremity of the s. cinguli (*d*). The sulci marked 21 and 29 in the right and left hemispheres respectively appear to belong to the post-central system, so that the inferior division of this sulcus is seemingly duplicated on both sides, as occasionally occurs. The furrows marked 20, 24 and 30 in the left hemisphere may perhaps be regarded as lateral branches of the s. post-centralis. The sulcus marked 20 on the left side (and more doubtfully that marked 15, 15, on the right) might be looked upon by some as constituting a form of *s. retrocentralis transversus* of Eberstaller, although rather shallow for this sulcus and placed somewhat high up in the hemisphere. Whatever name is given to this furrow there can be little doubt that, as Cole [8] has pointed out, a similar sulcus is of importance in the causation of the appearance of a large inferior Rolandic genu. Such a sulcus, as in this specimen, is usually better marked in the left hemisphere than in the right, presumably owing to the greater length of the posterior limb of the Sylvian complex in the former hemisphere.

The *sulcus interparietalis.* On the right side this consists of two independent portions, an anterior and longer (*l*) which is joined to a furrow taken to represent the middle part of the post-central sulcus, and a posterior and shorter (*e*), the *pars occipitalis* or *paroccipital sulcus* of Wilder. Behind the latter is a well marked *s. occipitalis transversus* of Ecker (m, m^1). The sulcus numbered 25 in front of the sulci *e* and *m* may perhaps be regarded as a duplication of one or other of these furrows such as sometimes occurs in complex brains. In the left hemisphere the anterior division of the s. interparietalis is in two separate parts (*l*, *l*), the posterior of these being much shallower than the anterior. The posterior division of the sulcus *e* passes backwards and then rapidly downwards and backwards to join a typical s. occipitalis transversus (m, m^1). The branch marked 17 behind the latter may probably also be regarded as belonging to the *m* system.

From the upper side of the s. interparietalis in both hemispheres springs a well marked branch, the *ramus medialis primus* (T). The *ramus medialis secundus* (e^1) is short and deep, as is sometimes the case. It is typically placed on the left side, but is not so readily identified on the right.

From the under side of the *l* portion of the s. interparietalis in the right hemisphere arise three *rami ventrales* (*v*, *v*, *v*). The anterior of these is rather unusually well developed and forms a boundary between the supra-marginal and angular gyri. On the left side two ventral rami spring from the sulcus *l* and one from the sulcus *e*. The anterior of these in this hemisphere also is a long furrow.

The other sulci of this region can be more conveniently dealt with when considering the temporal lobes.

The mesial surface of the parietal lobes. Right hemisphere.—Whilst the posterior third of the precuneus is almost smooth, the anterior two-thirds are unusually complex. The lower sagittal division of the K system of sulci (the *s. subparietalis*) joins anteriorly the s. cinguli (see fig. 2*b*). The sulcus is much branched and cuts off the greater part of the precuneus from the gyrus cinguli.

Above this sulcus are two more transversely directed furrows (K27 and 17) such as one may find in this region. These may be regarded as *sulci præcunei*. The upper part of the anterior of the two sulci we think, however, forms a furrow which sometimes runs into or becomes a *sulcus parietalis superior* of Retzius. Reference is again made to this sulcus on p. 60.

Left hemisphere.—The precuneus is more simply and uniformly convoluted than on the right side. The branches of the K system are quite independent of each other and of other sulci. The two lower of these form a *sulcus subparietalis*, but broad annectants pass between the precuneus and gyrus cinguli. The remarks made concerning the sulci K 27 and 17 of the right hemisphere apply also to the sulci marked K 33 and 25 (for sulcus 25 see fig. 4*b*) in this hemisphere.

The Temporal Lobes.

The superior surface.—On the right side one very long anterior transverse gyrus of Heschl is separated from two smaller posterior gyri by a deep sulcus, the outer part of which cuts into the greater part of the breadth of the first temporal gyrus. In the left hemisphere there are only two transverse gyri of Heschl, a long anterior gyrus separated from a shorter posterior one by a sulcus which indents the edge of the lobe.

The lateral and inferior surfaces. Right hemisphere. The sulcus temporalis superior, a.—This consists of two separate parts. The anterior of these is placed relatively unduly close to the edge of the lobe and is deflected in the hinder part of its course towards the Sylvian fossa, so that the anterior part of the first temporal gyrus is narrow. Occasionally this deflection of part of the superior temporal sulcus is complete, the branch turning right into the Sylvian depths. Such complete deflection, when present, appears to be much commoner on the left side than on the right. It is regarded by Mickle [15] as a departure from the usual, which, other things being equal, is in the direction of increased formative activity, and, although a deviation from type, is yet not necessarily a sign of inferiority. But there are other considerations which lead one to suppose that the condition may sometimes mean the persistence of an occasional fœtal tendency.

The posterior division of the sulcus is deep, and along its course several broad, deep annectants occur. It inclines away from the line of the Sylvian fossa, giving great breadth to the hinder part of the first temporal gyrus. This part of the sulcus sends off spurs upwards and downwards, and ends posteriorly in a bifurcation, forming a long anterior ascending limb (a^2) and a shorter posterior branch (a^1). The anterior branch, a^2, would probably be identified by Elliot Smith [10], and also by Kükenthal and Ziehen,[1] as the *sulcus gyri angularis*, although Zuckerkandl [25] (and also Bolk [3] for the gorilla) would regard the posterior branch a^1 as representing this sulcus. Kohlbrugge [12] and [13] does not name a determined furrow a sulcus gyri angularis. The reasons for the identification of the anterior branch as the sulcus gyri angularis are, as Dr. Cole suggests, that it is the original continuation of the main part of the sulcus temporalis superior, and that it is found in the older cortex (in which the sulcus first appears) common both to apes and man, whereas the posterior branch is situated in, or near to, the newer cortex further back. As is well known, modern histological research has thrown much light on the order of development of the inferior parietal lobule, and the point above alluded to is but another illustration of the fact that the identification of sulci on the ground of mere topical considerations is apt to be fallacious.

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[1] We have been unable to obtain access to Kükenthal and Ziehen's original work, and are only acquainted with their views in so far as they are discussed by the authors quoted.

The horizontally directed branches marked 12, a^1, and 15 may perhaps be regarded as forming a *s. parieto-temporalis* of Elliot Smith, partially separating the inferior parietal lobule from the temporal lobe.

The *sulci temporalis medius* (*i*) and *inferior* (f^1). The different divisions of these sulci have a fairly typical disposition, and are mostly separate from each other, although some of the posterior branches of the sulcus f^1 join to almost entirely insulate a considerable area of smooth cortex. In the more simply convoluted human brains the s. temporalis inferior is often closely associated with the s. collateralis—an indication of a reverting tendency. In this hemisphere these furrows are widely separated. The sulci of the lingual lobule are simple and shallow.

The sulcus marked *b* (also 19) appears to form a *s. occipitalis inferior* of Wernicke and Elliot Smith.

The *s. temporalis transversus* of Retzius, which commonly forms a fairly definite boundary to a distinct histological area (area temporopolaris (38) of Brodmann and of Elliot Smith), is represented by a posterior transverse branch of the anterior segment of the s. temporalis medius.

The lateral and inferior surfaces. Left hemisphere. The sulcus temporalis superior, a.—This sulcus is complex and is made up of several irregular branches, but the first temporal gyrus is of more uniform width than in the right hemisphere. The part of the sulcus behind and below the posterior Sylvian termination is broken up and is unusually shallow. Hereabouts also it joins with other furrows to almost entirely insulate a slightly depressed area of cortex. Behind this shallow split-up portion the sulcus divides into two terminal rami. The anterior of those a^2 may probably be looked upon as a *sulcus gyri angularis*. This sulcus is shallower than is the corresponding one of the right side, but it is longer and reaches to within about 20 mm. of the superior border of the hemisphere. The horizontal portion of the sulcus marked a^1 forms together with the sulci lettered *b*, *b* a very typical *s. parieto-temporalis* of Elliot Smith, although the latter elements (*b*, *b*) may be regarded as a *s. occipitalis lateralis* of Eberstaller. The K shaped sulcus marked a^1 9, immediately above the posterior ascending terminal ramus a^1, appears to form a *s. occipitalis anterior* of Wernicke.

The *sulci temporalis medius* (*i*) and *inferior* (f^1). The branches of these sulci are fairly typically distributed, but are very numerous. Many are separate the one from the other, and are much forked and spurred, rendering on the whole the lateral and inferior aspects of the lobe markedly complex in pattern. One of the branches of the sulcus f^1 almost joins the s. collateralis. The *s. temporalis transversus*, apparently composed of transversely directed branches of the superior and middle temporal sulci, is more irregular than is the corresponding sulcus of the right hemisphere. The deep sulcus marked f^1 (also 45) is apparently a *s. occipitalis inferior* of Wernicke and Elliot Smith.

The Occipital Lobes.

The external surface.—The furrows of the mesial aspect of these lobes are fairly typical in distribution, but the arrangement of the sulci on the external surface of the lobes in this specimen, as is not infrequently the case, is not easily reconciled with any of the recognized descriptions of the sulci of this region. Dr. Kohlbrugge has been kind enough to letter the sulci of this region in these hemispheres according to the system used by him, and he has made the following observations:—

In every large brain a duplication of sulci may be seen, especially in the parietal and occipital regions. The sulcus *b* (which we have referred to as forming a *s. occipitalis lateralis* of Eberstaller) may be doubled in one or both sides. In this specimen the sulcus is tripled in each hemisphere. If the sulcus *b* is doubled the sulcus *x* is likely to be duplicated also, as in the right hemisphere in this case, the lower branch probably belonging to the *i* system (s. temporalis medius). In the left hemisphere this sulcus appears to be like a duplication of sulcus *b*. The sulcus *x* is also double and united with the *b* sulci in both hemispheres. The sulcus *u* is single on the right side but duplicated on the left. No sulcus which has the typical direction of a *s. paramesialis* is present in either hemisphere.

Remarks on the Parietal, Temporal and Occipital Lobes.

The general size of the parietal and temporal lobes of both hemispheres appears to be about normally proportionate to that of the remainder of the hemispheres. The lateral surface of the occipital lobes, however, strike us as being relatively somewhat small in both hemispheres, although the latter well covered the cerebellum in the natural state. This relative smallness of the occipital lobes is by some regarded as an indication of good cerebral development, although, on the other hand, relative defect in size of these lobes is not infrequently seen in inferior brains.

The parietal lobes.—The post-central gyrus, especially in its upper and middle parts, is rather broader on the left side than on the right, and is more split up by cross sulci. This, however, is a common and presumably normal difference between the two hemispheres.

Owing to the different position in the two hemispheres of the component parts of the sulcus interparietalis and of the Sylvian fossa, there are certain differences on the two sides in the shape, and to some extent in the size of the superior parietal lobule and of the several parts of the inferior parietal lobule. But these differences are usual ones and doubtless quite within normal limits. Thus, whilst the supramarginal and angular gyri cover much the same extent of surface in the two hemispheres, on the right side the portion of the former gyrus in front of the posterior ascending Sylvian ramus is much narrower than is this portion in the left hemisphere, but the deficiency in this direction is mostly compensated for by an increase in height. The reverse applies, though to a less extent, to the angular gyrus, i.e., what this gyrus lacks in height in the right hemisphere is compensated for by increase in breadth. The post-parietal gyrus of the right hemisphere is distinctly larger in every direction than that of the left. The superior parietal lobule is of a very uniform breadth on the right side, but on the left lobule is broader in front and narrower behind as compared with its fellow of the opposite hemisphere.

It is of interest from the evolutionary aspect to note that the posterior part of the inferior parietal lobule—a region of the human brain which, according to Flechsig [11], is very late to myelinate, and which is relatively small in apes—is exceedingly well developed as regards size and complexity in both hemispheres, but especially so in the right.

The hinder part of the superior parietal lobule and of the precuneus appears to be large as compared with the fore part, particularly on the right side. This is also of developmental interest. As Cole [8] has pointed out, “the sulcus parietalis superior probably marks the boundary between an area of earlier myelination in front and an area of later myelination behind. The area in front is a region which attains a high degree of development in the gorilla." In this specimen the anterior and superior sulci of the K system (K27 on the right side and K33 on the left) are probably the furrows partly separating these two areas, which, according to Flechsig [11], myelinate at different dates, as probably also they do the *area parietalis superior* B from the same named area A of Elliot Smith, regions which this observer [10] believes to be structurally distinct. In these hemispheres the region behind the sulci just referred to is of large size as compared with the region in front.

As regards their convolutional pattern the parietal lobes in general may be said to be markedly complex, and the sulci are for the most part developed on regular lines. Secondary spurs are numerous and many of the sulci are much curved, but some, especially of the inferior lobules, are relatively rather shallow. Attention has already been directed to the apparent duplication of certain sulci, particularly in the right hemisphere; in fact the latter hemisphere appears, on the whole, to be more complex than its fellow.

Duplication of the ordinary furrows Mickle [15] appears to regard as abnormal, as being indeed a perversion of developmental activity excessive in degree, but lower in kind or grade, ill-directed and aberrant. But it seems to us that if this duplication has occurred in a regular manner—as in most places in this specimen—it should be looked upon rather as a sign of superiority, especially as it is apt to occur in all hemispheres of a highly complex convolutional pattern.

The tendency to separateness of the different elements of the post-central and interparietal systems of sulci, especially on the left side, might be regarded by some as an indication of under persistence of fœtal characters owing to developmental failure, but judged by the context, i.e., by the complexity of the hemispheres generally, we consider that this should more probably be looked upon as a sign of increased formative activity in the direction of superiority.

In neither hemisphere is there any tendency to the formation of what Mickle [15] has termed a reversed occipital or posterior parietal operculum. This author regards such an appearance as a manifestation of over-activity on the part of the parietal with some relative defect of activity of the occipital region. The absence of such a formation in this specimen can probably be accounted for by the fact that the developmental activity of the occipital lobes, judging by the duplication of many of the sulci of their outer surface, has been as great, or almost as great, as that of the parietal.

The Temporal Lobes.

These appear to call for little comment. The different sulci are on the whole well developed, so that the several gyri are fairly distinctly marked off from each other. The left temporal lobe is decidedly more complex in pattern than the right, secondary spurs and forkings of the sulci being more numerous in the former hemisphere. This difference between the temporal lobes of the two hemispheres of the same brain is probably not uncommon.

The somewhat aberrant direction taken by the first part of the s. temporalis superior in the right hemisphere has already been mentioned.

There is an even more marked tendency to separateness of the different elements of the sulci of the temporal lobes than of the parietal lobes, and we think that the interpretation which was placed upon this in the instance of the latter lobes applies also to the former. At the same time we consider that there is greater irregularity and aberrancy of the sulci in the temporal regions, on the whole, particularly on the left side—as shown by the numerous spurs, forkings and tendency to insulation of areas of cortex—than occurs in any other part of the hemispheres.

The external parieto-occipital annectant gyri.—There is no clearly recognizable *sulcus lunatus* of Elliot Smith in either hemisphere, and sulci which may be regarded as homologous with an "affenspalte" are difficult to identify. In the left hemisphere, however, it may perhaps be said that the sulcus marked 17 and the anterior part of sulcus *b* bear a similar relationship to the *s. occipitalis transversus* to that which the "affenspalte" bears to this sulcus.

On the left side the course of the external parieto-occipital annectant gyri can be traced with some definiteness. The first annectant passes round the extremities of the ascending limb (m^1) of the *s. occipitalis transversus* and of the *parieto-occipital fossa*, and is bounded anteriorly by a short processus acuminis (e^1) and by the dorsal continuation of one of the *precuneal* sulci. The second annectant, superficial and of considerable size, forms a loop round the end of the descending limb (*m*) of the *s. occipitalis transversus*, and is bounded in front by branch of the sulcus identified as the *s. occipitalis anterior* of Wernicke (a^1 9). The third annectant passes across and around the anterior end of the s. occipitalis lateralis of Eberstaller (*b*) and is bounded anteriorly by branches of the superior and middle temporal sulci.

In the right hemisphere the course of the parieto-occipital annectants is difficult to follow with any degree of certainty excepting that of the first which is a broad irregular gyrus passing round the extremity of the upper branch of the *s. occipitalis transversus* (m^1). But this gyrus is broken up by branches of the parieto-occipital complex and by sulci of the superior parietal lobule.

Zuckerkandl [25] has traced the course of the parieto-occipital annectant gyri in apes with much plausibility, but the attempt to identify these annectants in the human brain in every instance appears to us apt to lead to confusion. It seems by no means always clear which is which. In our experience the course of these annectants can not infrequently be more readily followed on the left side than on the right.

The insula; concealed areas of the frontal and parietal lobes. The limbic and olfactory lobes.—These parts, so far as can be seen without damage to the specimen, are, in both hemispheres, normally developed, have a size proportionate to that of the rest of the hemispheres, and show a convolutional pattern of at least average complexity.

SUMMARY AND GENERAL REMARKS.

(1) The cerebral hemispheres are of good general shape, and the different lobes of each hemisphere appear to bear about a normal proportion to one another, excepting that the occipital lobes are relatively somewhat small. The subfrontal region on each side is also rather small and simply convoluted, but the deficiency of this region is relative only.

(2) The convolutional pattern of the hemispheres as a whole is exceedingly complex, and in the distribution of the several sulci little beyond the following has been detected which can be regarded as definite marks of inferiority. The right *sulcus collateralis* may be said to be defectively developed, and some signs of reversion or aberrancy are shown by the *calcarine* sulci, and perhaps by the right *sulcus cinguli*. There are tendencies to insulation of areas of cortex in the right orbital region and in the temporal regions; also to irregularity and aberrancy of the sulci in the latter regions, particularly on the left side. Some indications of defective formation or aberrancy of sulci, however, are to be found, we believe, in almost every human hemisphere, no matter how good the development in general may be. The duplication and triplication of the sulci such as occurs, especially in the occipital and parietal lobes in this specimen, we prefer to regard, for the reasons given, as departures in the direction of superiority.

(3) Many of the sulci are much curved, and on the whole they certainly exceed the average normal in depth, whilst having a depth which, for the most part, is normally proportionate to each other. In places, however, the sulci are somewhat shallow; e.g., some of the furrows of the left inferior parietal lobule, a portion of the left sulcus interparietalis, and the posterior part of the stem of the left sulcus temporalis superior.

(4) Certain differences exist in the convolutional pattern of the two hemispheres. These have been fully detailed in the foregoing pages, and we consider that in most instances they are only such as are very commonly found between two hemispheres of the same brain, and that probably they can be regarded as normal differences.

PART II.—MICROSCOPICAL EXAMINATION.

The method of hardening the hemispheres employed and the reasons for this have already been stated. As it was desired to preserve one of the hemispheres as an almost complete museum specimen, the majority of the blocks for microscopical purposes were removed from the left hemisphere.

Sections, cut in paraffin, from the various regions were stained, after Nissl's method, with polychrome blue or thionin, and also for showing blood-vessels and neuroglia by the Heidenhain iron-hæmatoxylin method, followed by counter staining with eosin. The latter method fails to stain normal neuroglia fibrils—which is often an advantage—whilst giving an adequate display of all actively proliferating and abnormal neuroglia.

In all thirty-seven blocks were examined from the two cerebral hemispheres, twenty-nine from the left and eight from the right. It is unnecessary to detail the regions from which these blocks were removed, for the exact site of most of them is marked on the drawings (figs. 7 and 8) by a dotted line, against which a number is placed indicating the type of cortex found in the different situations. The numerals correspond to those used by Brodmann [6] in his map of the distribution of the histological areas of the human cerebral cortex.

The microscopical findings in this case are of interest from two separate points of view. Firstly, as an example of unusually large cerebral hemispheres, and secondly, as a case of epilepsy. From the latter aspect, the appearances which other observers, and particularly Turner [21], consider to be characteristic of epilepsy were carefully

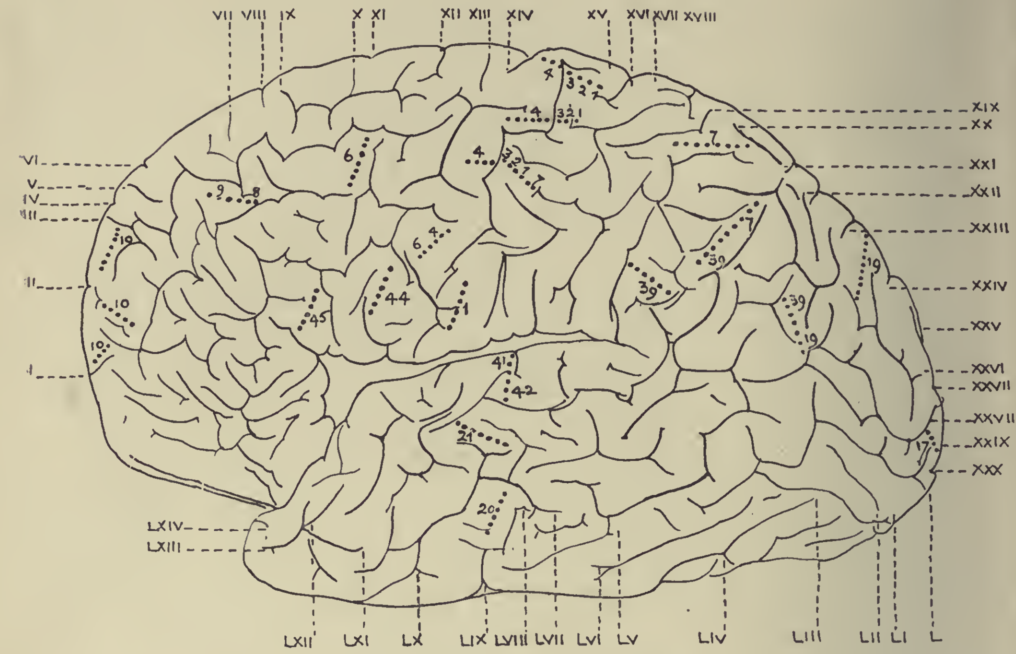

FIG. 7.—In this and the following figure the site of each of the blocks removed for microscopical examination is indicated by a dotted line. The numerals placed against these lines refer to the type of cortex found in the different situations, and correspond to those used by Brodmann for this purpose.

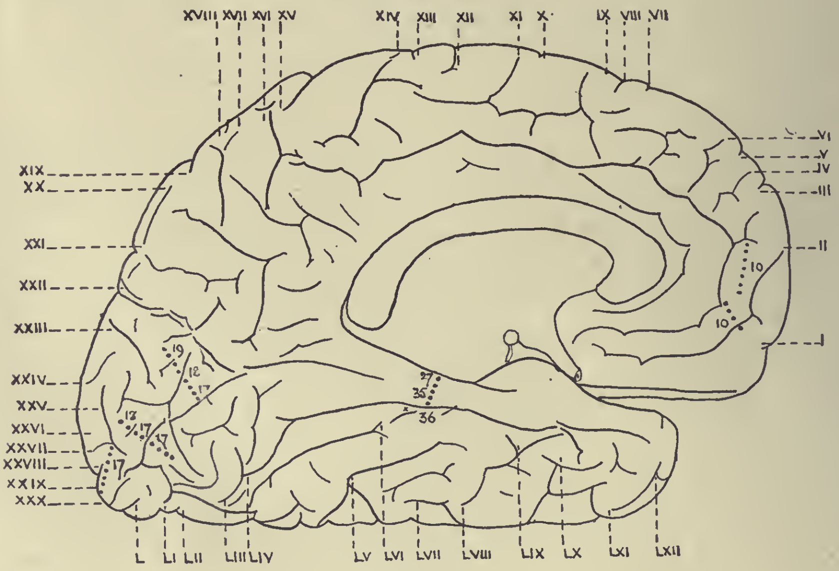

FIG. 8.

looked for during the examination of the sections. Allusion will be made to these in the course of the description which will be given under the following headings:—

(1) Types of cortex and their distribution.
(2) Structure of the cortex.
(3) Pathological changes.
  (*a*) The meninges.
  (*b*) The nerve-cells.
  (*c*) Gliosis and atrophy.
  (*d*) The blood-vessels—(i) structural alteration; (ii) perivascular and pericellular elements; (iii) congestion; (iv) intra- and extra-vascular clotting.

(1) *Types of Cortex and their Distribution.*

The different types of cortex found in all the regions from which blocks were cut are readily recognizable as usual to those regions, and in harmony with Brodmann's map of the distribution of the cortical fields of the human cerebral hemisphere, so that it may be said that the distribution of the different types of cortex in this specimen is normal, in at least so far as the hemispheres have been examined.

(2) *Structure of the Cortex.*

As regards its structure, the cortex of all the areas examined appears to be almost, if not quite, normal. The several laminæ of the cortex, so far as can be judged without micrometric measurement, are of good depth, and the individual nerve-cells are for the most part well formed. No cells were found in any region which could with certainty be described as under-developed, cells such as are commonly seen in cases of idiocy and imbecility. In the inferior parietal and middle temporal regions, however, the majority of the cells, particularly the smaller and medium-sized ones of the pyramidal layer, and many of those of the polymorphic layer, are somewhat globular or flask-shaped. As, however, degenerative change in the nerve-cells of those regions is considerable, it is impossible to state confidently that the shape of the cells, as above described, is due to congenital defect, and not to pathological alteration. At the same time it may be mentioned that, in our experience, under-developed cells are not infrequently met with in the brains of the insane in the inferior parietal and middle temporal regions, particularly in the latter.

The persistence of nerve-cells in the molecular layer, as seen by the ordinary staining methods and the presence of subcortical nerve-cells, are conditions usually regarded as stigmata of defective nervous development. In this case the only situation in which definite nerve-cells can be recognized in the molecular layer—and they are few in number—is the *para-insular* region, and the only one in which subcortical nerve-cells are present in any considerable quantity is in the anterior part of the *area frontalis granularis.*

The nerve-fibres, even by such an imperfect method for their display as that of the iron-hæmatoxylin method of Heidenhain, are seen in abundance, and, excepting where associated with areas of local atrophy, they have an apparently normal appearance. In particular, it may be stated that the tangential fibres of the molecular layer exist in great numbers, especially in those regions such as the central gyri and parts of the occipital lobe where normally their presence is readily demonstrable.

(3) *Pathological Changes.*

(*a*) *The meninges.*—Owing to the membranes having been stripped before the blocks were removed, only small portions of these can be seen along the sulci in some of the sections. When present, the meninges show considerable congestion, some fibroid thickening, and small-cell infiltration, but no hæmorrhages. A small amount of amorphous epicerebral exudate was found below the pia in one section from the left occipital region.

(*b*) *The nerve-cells.*—The nerve-cells show more or less marked degenerative changes, chiefly of a chronic nature, in the majority of the regions examined. With the exception of the Betz-cells of the precentral gyrus and the cells of the cornu ammonis, to which special reference will be made later, the cells most affected are the smaller, and to a less extent the medium-sized cells of the pyramidal lamina, although in places many of the cells of the polymorphic lamina are swollen and vacuolated. Nowhere, however, is any great loss of cells apparent excepting in a focus of atrophy in the post-central gyrus. The changes just mentioned, although not anywhere very marked, are most prominent in the following regions: the mid-frontal gyrus (*area frontalis granularis*); the inferior frontal (*area opercularis*); the middle and inferior temporal areas. They are next most marked in the prefrontal region (*area fronto-polaris*); the inferior frontal (*area triangularis*), and remainder of the frontal lobe examined including the precentral gyrus, and in the inferior parietal area. They are least evident in the various parts of the occipital lobe, in the post-central gyrus, in the gyrus of Heschl and superior temporal area, and in the para-insular and ectorhinal areas; in fact, the nerve-cells in many sections from the several last-named regions may be described as almost normal in appearance. It is of importance to note that in all parts where the nerve-cell changes are most marked, these changes are generalized rather than focal in nature, excepting in the area of atrophy of the post-central gyrus, to which allusion has been made. In certain parts where spaces exist between the nerve-cells, which might possibly be mistaken for areas of loss of nerve-cells, such spaces are normal to the type of cortex found in this particular region.

The Betz-cells.—These in all parts of the precentral gyrus examined are affected, and more so than the cells of the other laminæ of this region. Few, if any, of the hundreds of cells examined can be said to be normal; all show, at least, some chromatolysis, and great numbers of them have reached an advanced stage of degeneration. Many of the cells are swollen, whilst others are shrunken and are deficient in processes. Some cells stain deeply and diffusely, so that no definite chromophile elements can be distinguished. In the majority of the cells, however, the stainable substance is very deficient; the chromatolysis is sometimes diffuse or central, but in most cells it is of the axonal type. The nucleus of the cell is in some instances swollen, but more often it is shrunken; frequently it is displaced, and in many cells partially extruded. In view of the fact that the patient suffered from epilepsy, it is of interest to specially note that the affection of the Betz-cells is much greater than is that of the homonymous solitary cells of Meynert, in other regions which are for the most part practically normal in appearance.

(*c*) *Gliosis and atrophy.*—Sclerosis of the outer layer of the cortex is regarded by Bleuler [2] as characteristic of epilepsy, and in fact as an essential factor in the pathology of the disease. In this case a small amount of subpial neuroglial felting, forming a thin surface rim, is present in all the regions of the cortex examined, being most evident in the cornu ammonis and neighbouring subicular region, in the gyrus of Heschl, and in the para-insular region. In some parts also a few—usually a very few—proliferating glia-cells can be seen in the zonal layer. At no other level of the cortex, and in no part of the white matter in any region of the neopallium examined is there any definite proliferation of neuroglia, unless the moderate increase of the elements described below as "perivascular" and "pericellular" can be so regarded.

Turner [21] states that in none of his cases of epilepsy was the glial increase considerable—not indeed greater than is usual in cases of chronic insanity—and, if the cornu ammonis and gyrus dentatus be excluded, the same may be said with regard to this specimen.

The cornu ammonis.—Sclerosis of the cornu ammonis is regarded by many as highly characteristic of epilepsy (Worcester [24], Turner [21]). Turner found this condition in 48 per cent. of his cases, and he states that the microscropical appearances are chiefly of a negative character. "There is no increase of glia, the nerve-cells are few in number, and those present are generally degenerated, the vessels lie in wide lymph spaces and are collapsed and atrophied, or may have undergone hyaline degeneration. Small hæmorrhages are generally found in the cortex."

In this case the cornu ammonis appeared to the naked eye to be normal in both hemispheres. Only that of the left side was examined microscopically, and in this a very definite lesion was found, which, however, differed in appearance from that described by Turner [21]. In the cornu ammonis, gyrus dentatus, and to a less extent in the subiculum, there is below the condensed surface rim of glia already alluded to a marked generalized proliferation of glia near the surface and extending to a considerable depth, but there are no surface granulations. In addition to this, but separated from the more superficially proliferating glia is a deeper and extensive area of gliosis involving the greater part of the cornu ammonis and gyrus dentatus. In this area glia-cells are seen in all stages of formation. Most of them are giant cells, some with a large amount of lightly staining cytoplasm and with processes in various stages of condensation, others with a little darkly staining cytoplasm and numerous darkly staining processes. The glia-cells are massed chiefly around the blood-vessels and many processes are seen passing from them to the latter. The area appears to have started from several distinct foci. The nerve-cells of the stratum granulosum and stratum pyramidalium are in abundance, and although many of these are degenerated, they do not appear to have suffered any actual loss. The blood-vessels are not collapsed but well fill the lymph spaces, which are nowhere dilated. The vessel walls show only a moderate amount of hyaline degeneration and thickening. There is much congestion of the vessels, but there are no signs of intravascular clotting and no hæmorrhages. The condition is a definite gliosis, possibly following minute softenings, but of the latter there is no present evidence.

Several small areas of atrophy with little or no active gliosis are present. The largest of these is in the post-central gyrus near the top. It is an irregular wedge-shaped area involving all the laminæ of the cortex down to and including the granule layer. The atrophic patch contains a few scattered and stunted nerve-cells, and the lamination on either side of it is much disturbed, but there is little glial or vascular proliferation. Another area of atrophy was found in the precentral gyrus near the top. This is situated in the white matter and shows spaces crossed by swollen and varicose nerve-fibres. Other small areas of apparent atrophy without gliosis are seen in the white matter of the post-central gyrus, mid-temporal and prefrontal regions, but most of these are so minute that the possibility of their being artefacts cannot be altogether excluded.

(*d*) *The blood vessels.*—(i) *Structural alteration.*—There are no signs of endarteritis and the capillaries are practically normal. The only distinct change is some thickening and hyaline degeneration of the (microscopically) larger vessels. This varies considerably in different regions; it is usually slight and nowhere very marked. The vessels of the inferior parietal region are more affected than those elsewhere, not even excepting the cornu ammonis, and those of the right prefrontal region are rather more involved than those of the left.

(ii) *Perivascular and pericellular elements.*—The small perivascular elements are in general moderately increased in number. They adhere to the distal wall of the lymph spaces and are of various forms and staining reaction. Some appear to be lymphocytes and others, showing traces of cytoplasm, are probably neuroglia-cells, and possibly, as Turner [21] believes, mesoglia-cells of Ford Robertson. These elements are most numerous about the medium-sized vessels of the white matter and least prominent about the capillaries. There are no plasma-cells. The pericellular elements appear to be of a nature similar to the perivascular, and whilst nowhere very numerous, are most conspicuous in those regions showing the greatest amount of degeneration of the nerve-cells.

(iii) *Congestion.*—The veins and capillaries are intensely congested in most of the regions examined, but least so in the occipital region. The capillaries, owing to their engorgement, seem more numerous than normal. The distended veins, for the most part, completely fill the lymph spaces, but no varicosity was noticed. One or two minute capillary hæmorrhages were found in one block from the precentral gyrus.

(iv) *Intravascular and extravascular clots.*—In view of the important rôle which Turner [21] believes these clots to play in the causation of epilepsy, they were looked for with special care. Turner's thesis is that "epilepsy is a disease occurring in persons with a defect of the nervous system, either congenital or involutional, in whom also there is an abnormal state of the blood, characterized by a special tendency to clotting; and that the fits . . . owe their exciting cause to sudden stasis of the blood-stream in some (generally limited) portion of the cortex, resulting from the blocking of cerebral cortical vessels by these aforementioned intravascular clots."

Clots having features similar to those described by Turner as occurring with such frequency in epilepsy, and which he believes to be the result of a vital process, were found in some vessels in many of the regions examined. No fibrin formation was seen in any of the vessels, the clots taking the form either of minute round deeply staining granules or of larger, more or less spherical, hyaline bodies, or again of a finely granular fainter staining débris, sometimes immediately outside the vessels. The thrombosis, however, as seen by the staining methods used, was not anywhere very marked. In a given section from many of the regions perhaps only one or two vessels showed any evidence of intra- or extra-vascular clotting, and often this was slight. No thrombi at all were seen in or around the vessels in sections from the following regions; three out of five blocks from the left prefrontal region, the block from the anterior part of the area frontalis granularis, that from the upper part of the post-central region and all the blocks, excepting one, from the occipital and pre-occipital regions of both hemispheres. The clotting is slight but distinctly evident in all sections from the parietal and temporal regions excepting the middle temporal, where it is a fairly prominent feature. The vessels showing the greatest amount of clotting are, on the whole, those of the precentral gyrus, but even here much variability exists in different parts. The thrombi are more numerous in the vessels of the white matter than in those of the grey. On reference to the account of the regional distribution of the nerve-cell degeneration (see pp. 66, 67), it will be observed that there is no constant relationship between the severity of such degeneration and the amount of intravascular clotting as seen in the sections.

SUMMARY OF THE MICROSCOPICAL APPEARANCES AND REMARKS.

(1) The presence of a considerable number of subcortical nerve-cells in the anterior part of the area frontalis granularis, and of a few nerve-cells (seen by ordinary staining methods) in the zonal layer of the para-insular region, together with the somewhat more doubtful existence

of under-developed nerve-cells in the inferior parietal and mid-temporal regions, are the only evidences found of defective nervous development.

(2) Otherwise the cerebral hemispheres, so far as examined, appear in every way to be normally constituted, and their great size and weight cannot be accounted for by the very slight increase in neuroglia and thickening of the vessels which existed.

(3) Certain abnormalities were found, however, which are obviously the result of pathological change.

(*a*) The lesion of the Betz-cells is remarkable in that almost all the cells examined are more or less profoundly affected, in great contrast to the condition of the great majority of the homonymous solitary cells of Meynert in other regions. The presence of an immature form of Betz-cell, characterized by its similarity to that seen in an early stage of axonal degeneration, is regarded by Turner [21] as an expression of congenital defect of the nervous system, which is of primary importance in the etiology of epilepsy. In our experience Betz-cells, either of an axonal type or otherwise congenitally defective, are almost constantly found in the precentral gyrus of idiots and low grade imbeciles, whether the patients have suffered from epilepsy or not. But it may well be that in this case, and probably in other cases of epilepsy occurring in subjects whose brains are apparently not at all, or only slightly, congenitally defective, the appearances seen in the Betz-cells are of a degenerative nature, the result of prolonged exhaustion occasioned by the epileptic discharges. One of us at least (J. W.) inclines to the view that the *fons et origo* of epilepsy must be sought for in the instability, and consequent loss of control, on the part of the higher motor nervous arrangements rather than in the congenital defect of the Betz-cells themselves.

(*b*) Other morbid changes, particularly in certain areas, and affecting especially the smaller and medium-sized cells of the pyramidal layer, are present, but these appear, for the most part, to be the expression of a generalized degeneration process rather than focal lesions due to local vascular occlusion. A certain number of limited areas of atrophy, however, do exist—one in the grey matter of the post-central gyrus and others in the white matter of various parts—but these, although of interest as local changes, are not numerous, considering the number of sections examined, and as compared with their frequency in the cases of epilepsy described by Turner [21].

(*c*) Apart from the area of pronounced gliosis found in the cornu ammonis the amount of glia proliferation is not greater than that commonly seen in cases of chronic insanity.

(*d*) Evidences of intravascular and extravascular clotting exist in many of the regions examined, but no definite correlation between the extent of this and the amount of neuronic degeneration could be determined.

Part III.—General Remarks and Conclusions.

The pathology of hypertrophy of the brain appears to be very imperfectly understood, and there seems to be little object in discussing the matter fully here, as in this case nothing has been found which throws light on the subject.

Cases of so-called cerebral hyperplasia may be divided into at least two distinct classes, unilateral or localised and general.

Apparently four cases of hyperplasia of one cerebral hemisphere have been recorded, notably one by Douglas Webster [23], who gives an account of the literature of the subject generally, and to whose paper we are indebted for some of the following particulars:—

In Webster's case there was also unilateral hypertrophy of the body and an acromegalic condition of the feet. Numerous glia-cells were found in the left insular region of the brain, one of the specially hypertrophied parts, and the left cerebral hemisphere was as a whole more richly vascularised than the right.

In a case reported by J. Batty Tuke [20] there was co-existent atrophy of the left side of the body and considerable glial increase especially in the left occipital lobe of the brain.

Our case falls into a different category and appears more closely to resemble an instance of general hypertrophy of the brain, recorded by Anton [1], in which few or no pathological changes were found apart from those usually associated with epilepsy.

Various conditions have been assigned a causal relation to the cases of cerebral hyperplasia reported. Amongst these the following appear to be the most important, although trauma, lead-poisoning, enteric fever and rickets have also been discussed.

Heredity, as in van Walsem's [22] case of an epileptic idiot, aged 21, who had two macrocephalic brothers.

Hydrocephalus: an acute hydrocephalus is suggested as a possible cause of the hypertrophy in Tuke's case.

Disturbances of internal secretion: Anton [1] discusses the relationship of the adrenals to cerebral malformation, but these organs, examined microscopically in Webster's case, appeared to be normal, as also was the hypophysis cerebri, except for some increase of the chromophile cells.

Hyperæmia: Webster [23] suggests as a more probable cause in his case vasomotor disturbance of one side of the body, particularly of the internal carotid artery and its branches.

Cases of very pronounced macrocephaly are of such comparative rarity that we think the record of our case may prove of interest even though the origin of the matter still remains obscure. None of the conditions which have assigned a causal relationship in this connection appear to have been present. The internal secretory glands were unfortunately not preserved for microscopical examination, but to the naked eye these all seemed to be quite normal.

The brain, although one of the heaviest on record, is, as will have been gathered from the detailed description, for the most part normal in appearance differing from the average brain mainly in its increased size and complexity of pattern. The microscopical changes found also do not at all necessarily bear upon the question of cerebral hypertrophy, being merely those usually present in the brains of chronic epileptics. On one point, however, the microscopical examination gave definite, although negative, results. There is no general hyperplasia of the neuroglia such as has been considered to form the basis of the cerebral hypertrophy in some cases.

Although there are some indications in places of defective development of the sulci and of reverting tendencies, these are not numerous, nor are they pronounced, probably not more so than are such indications in the majority of human brains, even in those which may be described as generally well developed.

There are, however, in the cerebral hemispheres many signs—apart from their large size—of a formative activity much greater than that usually seen. But we think that this increased developmental activity has proceeded, for the most part, on regular lines, and that on the whole the departures from the ordinary in the convolutional pattern of the brain are in the direction of superiority. On the other hand, the tendency to insulation of areas of cortex, and the marked spurring and forking of certain sulci, such as is seen particularly in the left temporal region, may probably be looked upon as indications of formative activity on irregular or aberrant lines. With this greatly increased developmental activity, whether in the direction of superiority or of aberrancy, it seems likely that there would be a tendency to instability.

It is of interest to note, in this connection, that unlike many other recorded cases of this class, the patient was neither idiotic nor imbecile, but was originally of at least average general intelligence, with special ability in music. Epilepsy, as in this instance, is a frequent complication of these cases, and this suggests the idea that even when the minute structure of the brain appears to be normally constituted—which it by no means always is in such cases—the usual size of the brain, apart from its increased complexity of pattern, cannot be largely exceeded without introducing a condition of instability which renders its possessor liable to suffer from some form of nervous breakdown, and especially from epilepsy.

REFERENCES.

[1] Anton, G. *Wien. klin. Wochenschr.*, 1902, Bd. xv, S. 1321.

[2] Bleuler. *Münch. med. Wochenschr.*, 1895, Bd. xlii, S. 769.

[3] Bolk, L. *Zeitschr. f. Morphol. u. Anthropol.*, 1910, Bd. xii, S. 141.

[4] Bolton, J. S. *Arch. of Neurol.*, 1903, vol. ii, p. 424.

[5] *Idem.* "The Goulstonian Lectures," *Brain*, 1910-11, vol. xxxiii, p. 26.

[6] Brodmann, K. *Journ. f. Psychol. u. Neurol.*, 1902-07.

[7] *Idem.* "Vergleichende Lokalisationslehre der Groszhirnrinde," Leipzig, 1909.

[8] Cole, S. J. *Journ. of Anat. and Physiol.*, 1910, vol. xliv, p. 315.

[9] Cunningham, D. J. "Contribution to the Surface Anatomy of the Cerebral Hemispheres," Royal Irish Academy, "Cunningham Memoirs," No. vii, 1892.

[10] Elliot Smith, G. *Journ. of Anat. and Physiol.*, 1907, vol. xli, p. 237.

[11] Flechsig, P. "Gehirn und Seele," Leipzig, 1896.

[12] Kohlbrugge, J. H. F. "Die Gehirnfurchen der Javenen," Amsterdam, 1906.

[13] *Idem.* "Die Gehirnfurchen Malayischer Völker vergleichen mit denen der Australier und Europäer," Amsterdam, 1909.

[14] Marchand. *Journ. of the Scientific Society of Saxony*, vol. xxvii; Abstract, *Centralbl. f. d. Physiol.*, 1902, Bd. xvi, S. 294.

[15] Mickle, W. J. *Journ. of Ment. Science*, 1896, vol. xlii, p. 541; *ibid.*, 1897, vol. xliii, pp. 1, 217, 462, 798; *ibid.*, 1898, vol. xliv, p. 17.

[16] Pfister, H. *Allgem. Zeitschr. f. Psychiat.*, 1894, Bd. l, S. 903; Abstract, *Journ. of Ment. Science*, 1895, vol. xli, p. 149.

[17] Sims (reference not personally confirmed). *Med.-Chir. Trans.*, 1835, vol. xix, p. 265.

[18] Spitka, E. A. *Trans. Amer. Phil. Soc.*, 1907, vol. xxi, p. 175.

[19] Symington and Crymble. *Journ. of Anat. and Physiol.*, 1913, vol. xlvii, p. 321.

[20] Tuke, J. B. *Journ. of Anat. and Physiol.*, 1873, vol. vii, p. 257.

[21] Turner, J. *Journ. of Ment. Science*, 1907, vol. liii, p. 1.

[22] Walsem, Van. *Neurol. Centralbl.*, 1899, Bd. xviii, S. 578.

[23] Webster, J. H. D. *Journ. of Path. and Bact.*, 1908, vol. xii, p. 306.

[24] Worcester, W. L. *Journ. of Nerv. and Ment. Dis.*, 1897, vol. xxiv, pp. 228, 263.

[25] Zuckerkandl, E. "Zur vergleichenden Anatomie des Hinterhauptlappens," *Arbeiten. a. d. Neurol. Inst. Wien*, 1903, H. 10, S. 297; also Leipzig and Wien, 1904.

THE RELATION OF THE MYOPATHIES.[1]

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THE classification of the myopathies is no easy task, but we may recognize two great groups of muscular atrophy or arrest, (1) the congenital, (2) the acquired.

The congenital embraces the cases of arrested growth in certain limited regions of the body, the infantile nuclear arrest ("Kernschwund") of Möbius. This muscular condition may be caused by defect of muscles with complete integrity of the nerve apparatus, or, on the other hand, the peripheral neurones may be much affected. The congenital arrest usually is not progressive, although it may be progressive in exceptional cases.

The acquired muscular atrophy also consists of two types, the primarily muscular, with intact nervous system, and the nuclear (neuronic), in which the nerve-cells of the peripheral neurones are affected. In the former we have the progressive muscular dystrophy, including the bulbar form of Hoffmann; in the latter we have the Werdnig-Hoffmann muscular atrophy, the infantile bulbar atrophy of Fazio, Charcot, and Londe, and the forms of myelopathy occurring later than the period of childhood. These types, as is well known, are progressive.

The various forms are combined in rare cases, and certain of the muscles of the body, as the pectorals and serratus magnus, show a special liability to arrest or atrophy in both forms. It is also well known that reaction of degeneration and fibrillary tremors, as well as changes in the cells of the anterior horns, have been observed in progressive muscular dystrophy, so that sharp distinctions cannot invariably be maintained.

The relation of muscular defect to progressive muscular dystrophy has been recognized by a number of investigators. By some the defect has been considered as arrested intra-uterine dystrophy. In persisting portions of arrested muscles the histological findings have been those suggesting intra-uterine muscular dystrophy, and yet one must be cautious in accepting these findings as conclusive, for it is questionable whether a decision can be formed as to the myopathic or myelopathic character of atrophy from the microscopical findings in the muscles alone. In a paper published in 1898, and in another published in 1900, I called attention to the fact, even at that time well known, that the distinctions which had been sharply drawn between "degenerative" and "simple" muscular atrophy were not trustworthy, and that the histological investigation of the muscles could not determine the myelopathic or myopathic nature of the atrophy [52]. Combinations of muscular defect with muscular dystrophy have been described.

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[1] This paper was laid before the Neuropathological Section of the International Medical Congress [August 9, 1913].

Recently we have had the classification of myopathy considered in an able article by Frederick E. Batten [3]. His classification affords an excellent basis for discussion. It is as follows:—

(1) The simple atrophic type (myatonia congenita or amyotonia congenita).
(2) The pseudo-hypertrophic type.
(3) The juvenile type (Erb).
(4) The facio-scapulo-humeral type (Landouzy and Dejerine).
(5) The distal type (Gowers).
(6) The myotonia atrophica type.
(7) Mixed and transitional types.

To these I add a somewhat questionable type:—

(8) The true hypertrophic type.

I shall have little to say regarding the types mentioned in the headings 2, 3 and 4; they have been the subject of innumerable papers by Duchenne, Erb, Landouzy and Dejerine, and a host of others. Their sharp limitation, however, is still a matter of dispute, and among recent writers on this subject may be mentioned Eulenburg and Toby Cohn [25]. These authors show by the report of five cases of dystrophy in one family that it may be impossible to class a given case under any one of the recognized types. They maintain that the types are useful for didactic purposes, but should not be too sharply insisted on, and with this view we must agree.

The simple atrophic type, as described by Batten, is one of the most disputed. It is congenital or begins in early infancy, and is characterized by smallness, lack of power and loss of tone in all the muscles of the body, without localized atrophy or hypertrophy of individual muscles or groups of muscles. All movements are performed in a feeble manner. The disease is slowly progressive, and, as a rule, walking is never learnt. The muscles are very flaccid, and the hands and feet can be bent at unusual angles to the arms and legs. Some contractions of the flexors take place late in the disease. With this type Batten assimilates amyotonia congenita, and unquestionably there are many points of resemblance. The distinctions, as Collier and Wilson [14] formulate them, are:—

(1) The myopathies are conspicuously familial diseases, whereas no familial tendency has been recorded in amyotonia.

(2) The several types of myopathy often show familial relationship one with another, whereas no case of amyotonia has been reported in the myopathic family.

(3) A large majority of the cases of amyotonia are congenital, the condition being obvious at birth. In a minority of cases amyotonia has appeared acutely and has reached its most severe degree in a few days. In none of its several types is myopathy present at birth, nor does it ever appear acutely or reach its maximum in a few days.

(4) The characteristic muscular flaccidity is not present in myopathy.

(5) The local muscular wasting that is a marked feature of myopathy is not present in amyotonia.

(6) The course of myopathy is one of progressive muscular weakness, that of amyotonia is one of progressive amelioration of the symptoms.

(7) Return of the deep reflexes after their persistent absence for months or years has been recorded several times in amyotonia, and has occurred in two of the cases reported by Collier and Wilson. Such a return of an absent deep reflex has never been recorded in myopathy.

To these distinctions we may add two presented by Collier and Holmes, viz.:—

(8) Affection of the periphery of the limbs, and especially of the intrinsic hand muscles, which is the invariable rule in amyotonia, is of the greatest rarity in any form of myopathy.

In comparison with this positive statement, Archangelsky and Abrikosoff assert that the feet and hands in amyotonia usually are affected in less degree than the central portions of the limbs.

(9) Amyotonia never spreads to regions previously unaffected. Slow spreading of the affection from muscle to muscle is characteristic of all forms of myopathy.

Batten attempts to show that amyotonia may be a family disease, and in support of this argument he refers to the two cases of amyotonia in children of one family reported by Sylvestri. He refers also to the three cases in one family recorded by Finkelnburg, in one of which a pathological examination was obtained. He adds that one of the children, D.S., recorded by himself as having the simple atrophic type, had a younger brother similarly affected, although at the time of publication he was ignorant of this. These facts, Batten thinks, dispose of the first two points raised, viz., they demonstrate that amyotonia may be a familial disease and may occur in a myopathic family.

Cassirer [11] does not regard the cases of Finkelnburg in discussing the familial occurrence of amyotonia congenita, and states that only Sorgente and Beevor have described cases occurring in the same family, and these, he thinks, are questionable cases. He refers, however, to Sylvestri's cases which presented the characteristic symptoms of the disease, but regards them as uncertain. Further in his article Cassirer speaks of the familial form as described by Collier and Wilson, but regards all cases as "nicht ganz einwandfrei." It may be well to make a brief reference to these cases here.

Batten gives Sylvestri's cases as follows: S. recorded two cases of amyotonia in one family, the first and fifth children; the second and third being healthy, the fourth being a cretin. A maternal aunt suffered from the Landouzy-Dejerine form of myopathy. The elder child, at the age of 16, is said to have presented a typical picture of Erb's juvenile form. Sylvestri's description of the later development of this child is somewhat obscure.

Sevestre's [51] cases: A child, aged 2½ months, had rom birth flaccid paralysis with atrophy of the four limbs and trunk, except the diaphragm. Two other children in the family had a similar disorder. The paralysis was almost complete.

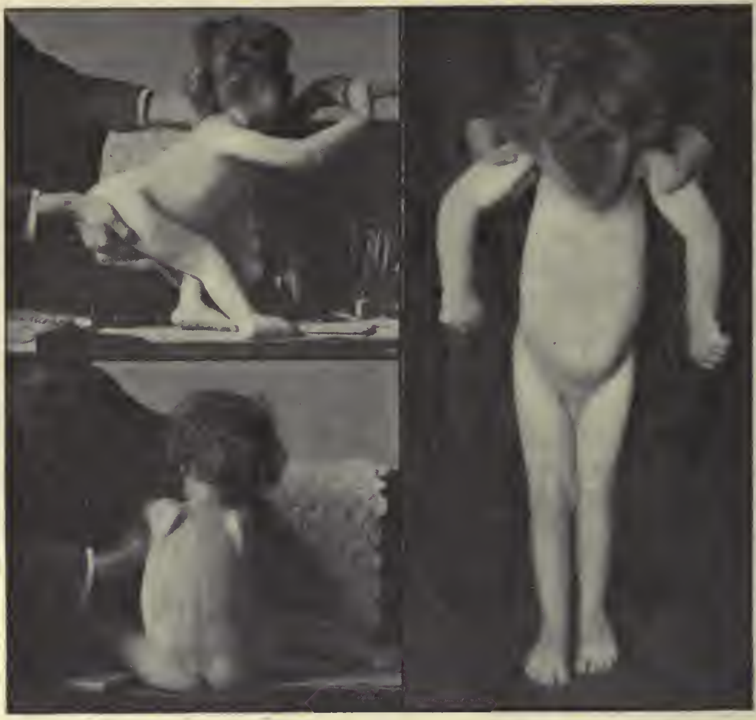
The cases of Sorgente, brother and sister, as given in abstract by Collier and Wilson, presented the symptoms of amyotonia, and apparently nothing contrary to the complex, unless possibly that there was no reaction in muscles of the legs to either faradic or galvanic current, and convulsions occurred before death. These were familial cases, and were without necropsy.

The case that Beevor described in Brain, 1902, was regarded by him as belonging to the Werdnig-Hoffmann type. It differed from this in that sensation was entirely abolished to the level of the second rib, and also in the age at which the symptoms began. The condition developed *in utero*, and the child died when it was nine weeks old, so that the disease in this family began earlier and was very much more rapid than in other recorded cases. Pathologically, the case was like the recorded cases in that the cells of the anterior horns were extremely atrophied, but it differed from them in that the posterior columns were degenerated. Other children in the family were affected.

The paper of Finkelnburg [26] makes the resemblance of certain cases of amyotonia, such as those of Spiller, Lereboullet and Baudouin, and Councilman and Dunn, to muscular dystrophy striking. As Finkelnburg says, in spite of the immense amount of work done regarding muscular dystrophy, anatomical investigation of cases in the first months of life did not exist previous to his study. A microscopical examination of dystrophic tissue in early life, he thinks, is of great value in the disputed question of neuropathic or myelopathic nature of the disorder. His case was as follows: A boy, aged 21 months, developed normally until the eleventh month, according to the mother's statement. He could sit alone at the sixth month, and attempted first to stand at the ninth month. At the eleventh month the mother noticed the child had lack of muscular tonicity. In sitting he sank forward, so that he must be held by the shoulder-girdle. One can hardly suppose from these statements that the child was normal until he was 11 months old; such weakness would be gradual in development. The disease must have been congenital or acquired in the first months. The calf and gluteal muscles were especially well developed, although very soft, in contrast with the atrophied upper arm and shoulder muscles. The limbs were weak, especially in the proximal parts. The tendon reflexes of the lower limbs were not obtained. The child lived only three days under medical observation. Two other children in the family had muscular dystrophy at the eighteenth and twenty-fourth month respectively. Carey Coombs's case of amyotonia is interesting in this connexion inasmuch as the upper limbs were more affected than the lower.

In this case of Finkelnburg there is much to suggest amyotonia from a clinical point of view. The findings suggested muscular dystrophy, but there were, on microscopical examination, fields composed entirely of very small muscle-fibres without increase of connective tissue between them. Finkelnburg thought these small fibres could not be considered as normal fibres in a state of development, as they were much smaller than they should be in a child of the age of his patient.

Councilman and Dunn, however, have shown that muscle-fibres vary greatly in size in children of the same age. Finkelnburg concluded that the small fibres were not atrophied fibres, but fibres arrested in their development, and their tendency to dystrophic change was shown in the presence of hypertrophied fibres among the small fibres. No changes in the nerve-cells were found.



FIGS. 1, 2, and 3.—Congenital weakness and hypotonia with "winged scapulæ" and "loose shoulders."

Dr. Langley Porter, of San Francisco, California, has given me the notes of a very interesting family in which the diagnosis between amyotonia and muscular dystrophy is not altogether easy. The disease is a familial one.

The parents of the children are healthy, and no similar disease is known in the ancestry. A maternal grandfather had syphilis. The family consisted of five children. The first child, a girl, is now aged 14, well developed and normal. The second child, a boy, had a condition which may have been amyotonia or muscular dystrophy with rickets. He had recurrent attacks of bronchitis, and died in one of these. He was never able to sit erect, to hold the head erect, or to raise the upper limbs above the shoulders. No electrical reactions were taken. The third child, a girl, now aged 9, is in perfect health. The fourth child, a boy, died a few days after birth, and possibly had an atonic condition. The fifth child, a boy, is now aged 3 and a few months (April, 1911), figs. 1, 2 and 3. He did not use his hands as infants do; he fixed his eyes on objects, but did not reach out to grasp. He did not hold up his head until he was more than a year old. He was not able to sit erect until he was 20 months old. He has never shown any inclination to stand. When 14 months old, he did not use his hands well; now he uses them very well. He has no power in the shoulder-girdle, and the muscles of this part, the erectors of the spine, and all the mucles of the hips and thighs are small, so that all these groups appear smoother and flatter than normal, though not distinctly atrophied. He has distinctly "winged scapulæ" and "loose shoulders." He can flex the feet to a right angle and move the toes freely. He sits on the buttocks and twists himself from side to side in moving over the floor. Hypotonicity is pronounced, so that the front of the thighs can be placed against the trunk. The boy is very intelligent.

In a letter received from Dr. Porter nineteen months after the above notes were taken, it is stated that the boy has shown steady improvement in power of all the muscles other than those of the shoulder and hip-girdle groups, and of the neck. He still has difficulty in supporting his head, especially when he loses its balance, at which time it drops on to the chest, but never rolls sidewise nor backward. He can hold himself erect if supported by leaning against some object, but has no power to stand independently. He is subject to frequent attacks of bronchitis, and it is evident that the respiratory musculature is weakened.

The weakness in this case was congenital; this fact and the progressive improvement convinced Dr. Porter that the case is one of amyotonia, notwithstanding the familial character of the disease. On the other hand, the marked weakness of the muscles of the shoulder-girdle, the winged scapulæ and loose shoulders are suggestive of muscular dystrophy. Remarkable for dystrophy is the congenital commencement and the hypotonicity, so great that the front of the thighs can be placed against the trunk. Whatever view may be entertained regarding this interesting family, it shows clearly that a diagnosis between amyotonia and dystrophy may be difficult.

It thus appears that it is impossible to maintain that in amyotonia there is:—

(1) Absence of any familial tendency in the incidence of the disease.

(2) Absence of any familial or ætiological relation with myopathy.

The question now to be answered is: Are there any cases of myopathy in which the disease was present at birth?

If Dr. Porter's case be one of myopathy, as I am inclined to believe, the answer to this question is in the affirmative. Finkelnburg's case was one of very early myopathy, and possibly earlier than is recorded. Kaufman Schlivek [49] reports a case of congenital myopathy. The anterior part of the arms was flat, soft, and flabby. The posterior part was better developed, but also soft and flabby. The shoulders and forearms were well developed. Active motion was limited at the shoulder; pronation and supination of the forearms was good. Motion in the wrists, hands, and fingers was normal. The muscles of the thighs and legs were soft and flabby. There was lordosis when the child stood, but not when she was sitting. Knee-jerks were present. Electrical reactions showed only quantitative change. The author considered and excluded amyotonia.

Russell Howard [37] reported a case of congenital defect of the muscular system (dystrophia muscularis congenita), and its association with congenital talipes equino-varus. The child was one of twins, and lived seven days. The report is a pathological one. The spinal cord was not examined microscopically, but peripheral nerves were examined, and were normal. The case was regarded as one of primary degeneration of the muscles occurring before birth. The writer believes congenital talipes may be a limited congenital muscular dystrophy.

It is doubtful whether either amyotonia or myopathy ever begins acutely or reaches a maximum within a few days. Batten thinks a development of this kind is rare, and the cases in which it has been recorded can hardly be taken as proof of its occurrence. He gives no references to any cases of this character, and states that it is admitted that an acute illness may bring into prominence symptoms which have not been observed previously; but it has not been proved that the true hypotonic condition of the muscles seen in typical cases of amyotonia is acutely produced.

Collier and Wilson, [14] however, assert that in three cases the condition came on rapidly, and reached its maximum within a few days of the onset of an acute illness in a previously healthy child. In one of their cases an attack of acute bronchitis was followed by complete paralysis within a week in a child aged 12 months, who had been until this time apparently healthy. In Leclerc's case a healthy child, aged seven weeks, was seized with broncho-pneumonia, and became paralysed generally within a few days, and though slow improvement had gone on all the time, four years later the case was typically one of amyotonia. In Comby's case the amyotonia came on rapidly, following an attack of diarrhœa at four weeks, and was almost universal in its extent, and severe in degree. Collier and Wilson say the histories of these three cases hardly admit of the explanation, that we are here dealing with the effect of an acute illness in bringing into evidence an amyotonic condition already present in minor degree, but it suggests strongly that an acute toxic process was the cause of the amyotonia.

Leclerc [41] was doubtful of the correctness of the parents' statement concerning the rapidity of the onset. He says the child appeared normal at first, but at the age of seven weeks had broncho-pneumonia and spasm of the glottis, and the muscular condition then developed. He asserts, however, that it was a typical case of amyotonia, that it was almost certainly congenital, even through the parents believed the spasm of the glottis indicated the onset of the amyotonia. He thought the parents overlooked the early condition. At all events, the increase of the symptoms seems to have been sudden and severe.

Comby [16] says of his case that the child was born at term and well formed. It was noted soon that the superior or inferior limbs, sometimes all the limbs, even the head, could not be moved freely.

It is doubtful whether these two cases can be accepted as demonstrating an acute onset of amyotonia, and the possibility of such an onset depends alone on the report of the case of Collier and Wilson.

We can hardly accept the case of Armand-Delille and Albert Weil [1] as one of myopathy, even though it was so regarded by them and by Raymond. The rapidity of development and the recovery make the diagnosis very questionable.

The acutely developing cases of amyotonia may be confused with anterior poliomyelitis and diphtherial palsy. Collier and Wilson say so far the acute cases have followed only acute bronchial disease. As a rule poliomyelitis may be distinguished, according to these writers, by the strict symmetry of amyotonia upon the two sides, the absence of local muscular atrophy, the absence of complete paralysis, and the absence of the rapid narrowing down of the extent of the regions affected which follows an attack of infantile paralysis. Granting that these points will enable poliomyelitis to be distinguished from amyotonia, there are cases of poliomyelitis in which there is symmetrical or nearly symmetrical and general implication of the lower limbs or of all four limbs, the wasting is general in the affected parts, the paralysis is complete in the affected muscles, and partial recovery is slight or absent. It is true that such cases are the exception, and that usually poliomyelitis can readily be distinguished from amyotonia congenita.

Diphtherial palsy may cause even more confusion should acute cases of amyotonia become more common. Collier and Wilson state that diphtherial palsy is very rare during the first year of life, when amyotonia usually develops. The absence of deep reflexes and the flaccidity may be in both, but the presence of nasal regurgitation and of cardiac debility, and the history and cause of the diphtherial palsy should render impossible the making of any mistake between the two diseases in the opinion of Collier and Wilson.

We can hardly dispute, however, that diphtherial palsy may occur with so little pharyngeal involvement that it may be overlooked, and nasal regurgitation and cardiac debility may not be conspicuous in all cases of diphtherial palsy. Again, it is to be remembered that the attempt is to be made to distinguish diphtherial palsy, rare in children of the first year, from an even rarer affection, acutely developing amyotonia.

Diphtherial palsy becomes especially important in connexion with Bernhardt's [9] views regarding amyotonia. He believes a multiple neuritis or an arrest in the development of the nerves is more likely to be the cause of amyotonia than an arrest in the development of the muscles. The improvement which occurs in this disease can be explained better on nerve disturbance than on muscle disturbance. He acknowledges that disease of, or deficient development of, the nerves in amyotonia has not been determined. He has shown that multiple neuritis may occur in the first years of life, and the cases he reports bear a striking resemblance to amyotonia. Slow contraction of the affected muscles in amyotonia by direct galvanic current, he says, was observed once by Oppenheim and in one of his own cases. We must therefore acknowledge that multiple neuritis developing in the first year of life, at least as early as the fourth month, may cause a clinical picture apparently indistinguishable from amyotonia, and the neuritis is not necessarily from diphtheria. In one of Bernhardt's two cases recovery strengthened the diagnosis of neuritis, as recovery would be less likely to occur in a disturbance of the muscles than in one of the nerves.

A case which I had the opportunity to study in Dr. Griffith's wards presented the appearance of an acutely developing muscular dystrophy, and is similar to the case reported by Armand-Delille and Weil. The complete recovery after some weeks suggests multiple neuritis, and yet pain was never a prominent symptom, and objective disturbance of sensation never occurred.

J. G. (figs. 4 and 5) was admitted to the University Hospital on March 19, 1912. His age was seven years. Two brothers and one sister were living and well, and no children had died in the family. The patient had not used alcohol, and alcoholic neuritis is very rare in children. He had had no symptoms of diphtheria. His teacher had noticed that he had been very dull mentally for two months. He had masturbated. He went to school until about six weeks before he came to the hospital, and he was then noticed to be walking slowly. He was said to have fallen on the steps three weeks before admission, and following this had pain in both lower limbs and the right upper limb. It was difficult to judge concerning the character of this pain. It did not appear to have been severe, and he had none when he came under the observation of physicians. It may have been from bruising of the muscles in the fall, or it may have been from use of weak muscles, and it is even possible that the statement concerning pain was incorrect. The weakness antedated the fall.

I found the pupils equal, and the irides reacting normally to light and in accommodation. The limbs were rather massive, suggesting the possibility of pseudo-hypertrophy. When he was placed at full length on the floor and told to raise himself, he turned over on the knees and palms of the hands, placed the right hand on the right thigh, but was unable to take the left hand from the floor and to raise the body above this position. When he was allowed to sit on the floor the muscles of the back at times were too weak to support him, and he fell backward and struck the head in the occipital region with great force. When he was lying in bed he could lift the lower limbs with difficulty, and could move them at all parts, but could not move them against slight resistance. The upper limbs were as weak as the lower, notwithstanding the apparently good muscular development. A brother of the patient, a little older, examined by me, was normal physically and mentally.

Extreme hypotonia certainly is not a common condition in myopathy, but Batten believes that marked flaccidity is present in many cases. I have never seen myopathy with the extreme hypotonicity of amyotonia, such as was present in my case of amyotonia, when the thighs

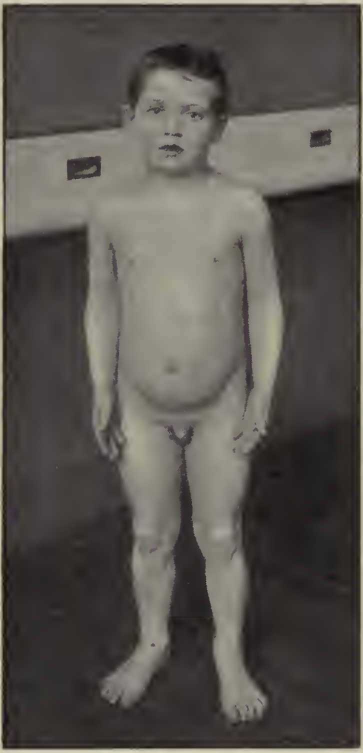


FIG. 4.—J. G. Excellent muscular development, but great weakness of rapid onset with recovery.

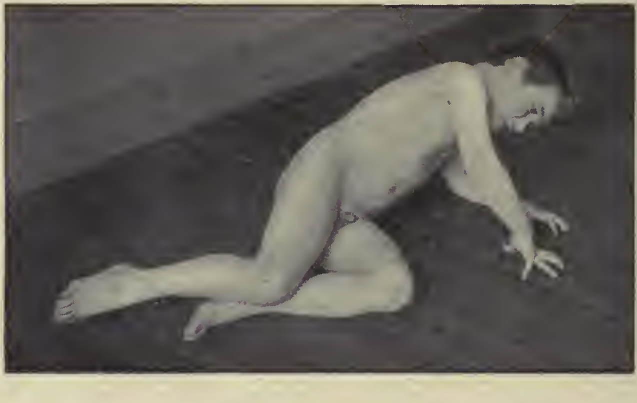


FIG. 5.—J. G. Showing attempt to climb on the lower limbs, as in pseudo-hypertrophic muscular paralysis. The photograph shows almost the full power of the boy. He was able to turn over a little farther than is represented, and to place the right hand on the right thigh.

could be placed close against the trunk and the heels behind the occiput; nor so intense as described by Collier and Wilson when they say that in several cases, including one of their own, the position which the foot assumed at rest was with the whole length of the dorsum of the foot lying along the front of the tibia. They state that the wrist and fingers can often be over-extended so as to come into complete contact with the back of the forearm.

Localized wasting is not always present in myopathy, and the atrophy may be general; still, localized wasting is a common feature of the early stage of myopathy, and its occurrence in amyotonia has not been observed. General wasting may occur in amyotonia, as in Thorspecken's case [57]. This case was typical in the absence of family disease, in the hypotonia, and of electrical reaction and in improvement. Atypical were general localization and symmetry of the paresis, the condition of the reflexes, muscular atrophy, the great atrophy of bone, and impairment of sensation, but this last-mentioned symptom seems doubtful. Cassirer says muscular atrophy does not belong to amyotonia, but Thorspecken finds smallness of muscles mentioned by many writers, and he thinks it is a fairly regular finding, and is masked by overgrowth of fatty tissue. The bone atrophy was found by the X-rays, and this method of examination has not been employed in other cases.

The untrustworthiness of progressive improvement in amyotonia as distinguishing it from myopathy is emphasized by Batten. As he says, in not a single case of amyotonia has recovery occurred; as the child develops, a certain gain of power has taken place, so that he may learn to stand or walk in a fashion. In Batten's case, D. S., improvement was said to be marked, but the boy could not stand alone, although he could do so with a little support. In many cases of amyotonia the condition has been progressive deterioration, not amelioration. In the case of amyotonia reported by Griffith and Spiller improvement for a time was marked, and this is remarkable in consideration of the pronounced and progressive changes of the nervous system, but, as in many other cases, the improvement was not permanent.

It is not because the period of observation in cases of amyotonia has been short that improvement is not great. In the case reported by Carey Coombs [17] the improvement after ten years was slight. The child was ten years old, and the condition had been present since birth. The upper limbs were more affected than the lower, and the hands were more affected than the rest of the upper limbs, so that there was localization in this case. In the study of any new disease experience teaches that certain statements may need modification, and that features considered sharply defined are of less importance than they at first seemed. Thus Collier and Wilson, writing in BRAIN (vol. xxxi, 1908), stated regarding amyotonia: "In no case has the least tendency to exacerbation of the disease been observed." In the next volume of BRAIN (vol. xxxii, 1909), these same authors, in reporting two cases, remark: "This is one of the only two cases that have come under our observation in which progressive deterioration has occurred." From the pathological point of view improvement appeared unlikely; they could detect no evidence of regeneration or of reparatory changes in the muscles.

On the other hand, myopathy may be arrested for a long period of years, or there may be improvement, usually temporary, and possibly obtained by enabling the patient to use the less affected muscles to better advantage, or by strengthening these muscles, or in rare instances recovery may ensue. Erb said he had seen only one case of recovery in myopathy. Marina's case he regards as not fully established as regards diagnosis. Erb's case [24] was a typical one of the juvenile type, and the patient was "practically cured" (as he expresses it) after six years, although some trifling defects remained.

Jendrassik [38] accepts Marina's case as one of myopathy, but he does not accept the case of Armand-Delille and Weil. He states that in Marina's case and also in Erb's the weakness was not great. He reports two cases of dystrophy with almost complete recovery. He says in all the cases the improvement occurred at the period of greatest physical development, i.e., at puberty; in Erb's, Marina's, and his own two cases the improvement occurred when usually rapid physical development takes place.

Gordon Holmes [36] reported a case of arrested myopathy. A man, aged 60, was found to have extreme weakness of the orbicularis palpebrarum of each side, slight weakness of the orbicularis oris, and the cheeks were remarkably flat and thin. Since he was 10 years of age he had not been able to whistle properly. The muscles which depress the arms were weak, and there was considerable wasting of the lower part of each pectoralis major, and atrophy of the upper portions of the trapezii. The man was unaware of the muscular abnormalities. His daughter and nephews had typical myopathy. Holmes regarded the case as one of myopathy which appeared early, but ceased to develop at a certain stage of its evolution.

Batten stated that in many cases of dystrophy it was admitted that there was evidence that the patients had had weakness of the face at birth, and when seen between the ages of 30 and 40 they still had the weakness of the face muscles, but no evidence of any progress of the disease.

Stanley Barnes has seen two cases of the Landouzy-Dejerine type; the patients were over 50, and in each there was no reasonable doubt that the pectoralis major had been absent for twenty-five years, and that the myopathy had not progressed for many years.

The only case of what seemed to be myopathy in which so great improvement occurred that it amounted to recovery which has come under my observation is the following: A man, aged 24, consulted me on October 27, 1904. None of his brothers or sisters had a similar disorder, although he had five brothers older than himself. He may have had typhoid in 1902, but it is not certain. When I saw him he had been complaining of weakness in the right lower limb about a year and a half. The muscles of the anterior part of the left thigh had seemed weak to him, but the weakness was not pronounced. During the three weeks before consulting me he had had moderate pain in the anterior muscles of the right thigh, probably from over-use of weak muscles, as he never had it before this time or later. He had lost about 25 lb. within the previous two years. He had much difficulty in walking, and could walk only a square or two.

On examination, the thighs were equally well developed, and measured about 16 in. in circumference in the middle. The right calf was large, and much larger than the left, which appeared atrophied. The circumference of the middle of the right leg was 13½ in.; of the left leg, 12½ in. The left calf was soft and flabby; the right calf was very firm. He could not stand on the right foot alone as he could on the left foot.

Flexion of the right thigh on the abdomen was somewhat impaired, and flexion of the right leg on the thigh and pushing with the right foot against the hand were a little impaired. The patellar reflex was present on each side, but was not very prompt. The Achillis reflex was hardly perceptible on the left side, and was lost on the right side. Sensation was not affected in any part of the body. The trunk, upper limbs, and face were not affected. Faradic contractility was prompt in the muscles of the left calf, but was lost in those of the right calf. Galvanic reactions were not taken. He was given massage.

This patient was last seen by me on June 13, 1912. The extraordinary firmness of the right calf had almost disappeared, and only a small mass of unusually firm tissue, about the size of an English walnut, remained. All weakness had disappeared, and he could walk fifteen miles daily with ease. The Achillis reflex was still lost on the right side. The patellar reflexes were nearly normal, possibly a little diminished. The peroneal supply on each side was unaffected.

The interesting features of this case were: weakness of the right lower limb, chiefly in the thigh, developing gradually during a period of one and a half years; possibly some weakness of the left thigh; apparently pronounced pseudo-hypertrophy of the right calf; atrophy of the left calf; diminished patellar reflexes; loss of Achillis reflex on the right side, and almost loss on the left side; absence of all objective and subjective sensory disturbances, except moderate pain in the right thigh in the weakened muscles of only three weeks' duration and probably from over-use; recovery during a period of almost eight years under massage and systematic exercise. The diagnosis of myopathy in this case would hardly have been disputed if recovery had not occurred. It is possible that typhoid fever may have been the cause of the weakness, and yet there was only an uncertain history of a disease that might have been typhoid; this had occurred two years before I saw him, and about six months before the onset of the weakness. The affection of both lower limbs made the diagnosis of thrombosis improbable. Hard patches in muscles are not uncommon in myopathy.

Typhoid fever may be a cause of myopathy, as Guillain has shown. He remarks that a few cases in literature have demonstrated the existence of true muscular hypertrophy as a result of typhoid. He gives the published cases to 1907 (Friedländer, Lesage, Cerné, Babinski). This enlargement of muscles appears to be a true muscular hypertrophy, with increased motor power, with diminution of faradic and galvanic contraction, without reaction of degeneration, and with exaggeration of tendon reflexes in certain cases, but not in all, and with limitation to one limb or part of one limb. The cause appears to be vascular lesions, especially phlebitis, and the condition an angio-myopathy.

Guillain distinguishes this hypertrophy from the functional or physiological muscular hypertrophy, the muscular hypertrophy of congenital myotonia, the muscular hypertrophy often associated with athetosis, the prodromic muscular hypertrophy of progressive atrophic myopathy, and the muscular hypertrophy of the hyperplastic muscular dystrophy of Talma.

In addition to this form of myopathy Guillain describes another form following typhoid fever, of progressive development and implicating many muscles, and he refers only to three cases: one of Friedländer, one of Josserand, and one of his own. The diagnosis of myopathy was confirmed by necropsy in Friedländer's case.

Guillain [32] believes he has observed many cases which demonstrate that myopathy may be acquired, and possibly from infection or intoxication. This is interesting in view of the cases of amyotonia developing acutely after pulmonary disease.

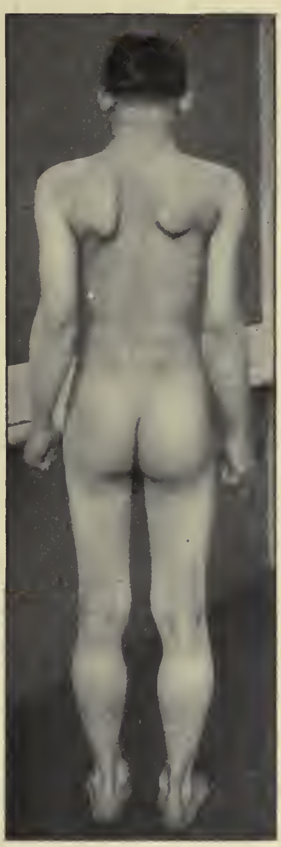


FIG. 6.—Myopathy with improvement. Atrophy of shoulder-girdle and upper part of upper limbs, "winged scapulæ."

I have known distinct improvement to occur in an advanced case of myopathy. E. S. (fig. 6) came to the dispensary of the University Hospital, on July 10, 1911. He was aged 19. A year previously he fell from a scaffold, a distance of sixty feet, and possibly struck on his shoulders. He was able to resume his work the same day, but the following day his arms were stiff and painful, and remained so for two days. From that time he could not lift anything heavy, and could do only light work. He noticed about four months later that the muscles of both shoulders were wasting, and that he had difficulty in using them. Since that time until the present the muscles have wasted, and he can raise the upper limbs to the level of the shoulders only. The deltoid, biceps, triceps, and pectoral muscles are much atrophied. No fibrillary tremors are observed. There are no sensory disturbances for touch and pain. There is no spasticity. The patellar reflexes are present, but not increased. There is no family history of similar trouble. A positive Wassermann reaction was obtained by Dr. Corson-White. Two brothers who were examined were normal.

I saw this man again in March, 1912. He was then under the care of Dr. John K. Mitchell. The atrophy conformed to Erb's juvenile type, and apparently had been started by the trauma, which is an interesting fact. No symptoms in the lower limbs suggested a cervical spinal lesion. Dr. Mitchell had ordered massage, and decided improvement had been obtained. There was distinct increase of power in the arms, hands, and legs. The man was able to comb his hair with his right hand, and this he had not been able to do before the treatment. He had found that the circumference of the upper limbs just above the elbows was 1 in. greater than it had been. He could raise the hands, when clenched, above the head. There probably has been no permanent arrest in the muscular atrophy, but important is the decided improvement in a case of myopathy, showing that improvement is not a feature of great value in the differential diagnosis between myopathy and amyotonia.

The failure of return of deep reflexes is common to both myopathy and amyotonia, and although return has been observed in the latter and not in the former, it is questionable whether great importance can be placed on this fact.

Failure of extension of the disorder from muscle to muscle in amyotonia at the present time appears as an important diagnostic sign, and yet who can tell how soon some one may report a case of amyotonia, with gradual spreading of the condition.

On the one side we have Batten urging the classification of amyotonia under myopathy, and on the other, Collier and Wilson and many others opposing this classification. Collier and Wilson remark that the similarity of the morbid anatomy of amyotonia to that of the myopathies is certain and does not admit of any discussion, but the clinical aspect of this disease is so widely different from that of any hitherto described form of myopathy as to warrant the retention of a separate name for what they call a distinct clinical entity. I have attempted to show in this paper that many of the so-called distinguishing features of amyotonia belong also to myopathy, but after all we must acknowledge that amyotonia has distinguishing features, observed in by far the greater number of cases, and that the cases with exceptions do little more than show that there may be a transition from amyotonia to myopathy, without proving that the two diseases are identical, any more than transitional cases between myelopathy and myopathy prove identity of disease.

There are a few cases of amyotonia which are typical clinically, and in which the lesions were confined to the muscular system; in order of publication these are the cases of Spiller, Lereboullet and Baudouin, and Councilman and Dunn. Possibly the case of Finkelnburg may be included. The pathology in these cases may be arrest in the development of the muscles with or without added muscular atrophy. Thorspecken [57] believes that not a single reported case of amyotonia can be regarded as one of arrested development, except possibly that of Archangelsky and Abrikosoff. In this case general and pronounced muscular atrophy of bone and contractures showed much resemblance to myopathy. Increase of connective tissue nuclei and of interstitial fat tissue are more in favour of disease changes in fully developed elements, but in my opinion do not exclude the possibility of arrest in development, at least as a part of the process. One may readily believe that tissue arrested in development would be more liable to degeneration.

In my case [53] increase of connective tissue nuclei and of interstitial fat tissue was relatively slight, and Councilman and Dunn in the report of their case show how difficult it is to judge of the intensity and importance of such findings. My case was a typical one of amyotonia, and although objection has been made to it by a few writers, it is very evident that some of these writers have never read my papers. It is impossible, for example, to reply to a statement that a case "nicht über allen Zweifel erhoben ist," or "nicht ganz typisch ist," but when Gött and Schmidt state that the child I described was idiotic and had strabismus and amaurosis, I can only reply that they know more about the patient than I do. There is no remark in my papers that suggests idiocy in this child, and I have shown by a statement from Professor de Schweinitz of the Ophthalmological Department of the University of Pennsylvania that the ordinary concomitant squint present in the case was not the strabismus from ocular palsy, and that it is very doubtful whether the child was blind. This case was carefully studied clinically and by microscopical specimens, and microscopical sections were made from various levels of the spinal cord, from muscles from the sole of the foot, calf, back of the trunk, and arm, and from peripheral nerves.

The case of Lereboullet and Baudouin cannot be rejected merely because convulsions occurred, and that during these convulsions the muscular atony disappeared. The patellar and olecranon reflexes were diminished, but not lost. The exaggeration of reflexes later in the course of the disease is not sufficient to exclude amyotonia, and it was probably the result of the convulsions. A child with amyotonia is not exempt from convulsions.

The findings in the case reported by Councilman and Dunn [19] were purely muscular. The amount of connective tissue was increased. Some fibres appeared like normal adult muscle-fibres, others were very small, and under low power appeared as accumulations of cells arranged in fasciculi. The nuclei in the small muscle masses seemed to be extremely numerous. The apparently great number of nuclei was due to the number of the fibres, and when a single fibre was followed along the nuclei were not more closely set than they were in the large fibres. Occasionally fibres were seen which were hollow, with fibrillæ at the periphery, presenting much the appearance of embryonic fibres. There was no general fatty degeneration of the muscles, but in certain muscle-fibres there was a large amount of fat. The connective tissue in the muscles was relatively increased, but it was uncertain whether there was an actual increase in this tissue. The spinal cord was practically normal.

There are other cases of amyotonia with pronounced muscular changes and comparatively slight alteration of the nervous system, such as those of Baudouin, and Archangelsky and Abrikosoff. It is well to remember that while myopathy usually is without marked alteration of the nerve-cells of the anterior horns, even when the disease has existed so long as in the case reported by Duchenne [22] in 1872, by Landouzy and Dejerine [40] in 1886, and by myself [54] with the pathological findings in 1900, still there are transitional forms in which moderate changes of the anterior horn-cells are detected.

The subject of degenerative changes occurring in the lower motor neurones in muscular dystrophy has been discussed by Gordon Holmes. [35]. He reports a case of this disease in which there was considerable diminution in number and size of the nerve-cells of the anterior horns and atrophy and diminution of fibres in the ventral roots. He refers to a number of similar cases in literature. He thinks that in his case and in the majority of the others there can be no doubt that the condition was acquired, and was not a developmental defect. The nature of the cell-changes, the slight secondary gliosis of the ventral horns, the definite evidence of loss of fibres in the ventral roots and peripheral nerves, and the increase of connective tissue in the nerves, make this certain. He rejects the theory of nervous origin for the muscular atrophy in these cases, because the histological changes in the ventral horns in his case appeared to be distinct from the degenerative cell-changes he has found in any of the many spinal amyotrophies he has examined, and the muscular affection exceeded them both in degree and extent. He believes the neural changes are secondary to the primary muscular disease. He does not know of any evidence of neural degeneration secondary to disease entirely limited to muscle tissue, but he thinks it is probable that when muscle fibres undergo complete atrophy and disappear, the functional, and probably secondary thereto the nutritional, equilibrium of the neurones which terminate in these fibres must be disturbed. The terminal branches of the axis cylinders left naked by the disappearance of the muscle-fibres probably will be injured and possibly destroyed by the connective tissue which proliferates secondary to the muscle disease. He refers to Baudouin's case of amyotonia congenita, and shows how closely it resembles the case he reported. Baudouin himself spoke of the muscular changes, "telles qu'on peut les voir dans les myopathies." Holmes says that the morbid anatomy of Baudouin's case was identical with that of a considerable number of undoubted cases of muscular dystrophy. He states that the origin in his case and Baudouin's must have been similar, as Baudouin believed the abnormal condition of the muscles could not be regarded as merely an arrest of development, and must have been an acquired condition. Owing to its intensity the muscular alteration of Baudouin's case could scarcely have been secondary to the simple atrophy of the ventral horn-cells, and its nature, too, was distinct from that of the neuropathic atrophies. It must be concluded, Holmes thinks, that the disease of the muscles was an acquired regressive affection, dependent probably on an intrinsic developmental anomaly. From the pathological and clinical points of view Holmes thinks Baudouin's case differs from one of myopathy only in the commencement during intra-uterine life. The clinical manifestations so closely resembled those of myopathy that it seems unnecessary to place the case in a separate class. The most important distinction of amyotonia is that it is not progressive, and that amelioration may occur. Even if amyotonia were congenital myopathy, these distinctions would not be surprising in view of the difference of the nutritional conditions of the individual before and after birth, and the changes in the mutual relationship of the muscular and nervous systems in intra- and extra- uterine life.

It seems probable to me that an arrest with later atrophy may occur in the peripheral neurones as well as in the muscles in some cases of myopathy. It is common to find more than one defect in development. Oppenheim has emphasized this as regards myasthenia. Cataract with muscular atrophy is another example. The case of myopathy of long standing referred to above shows that great destruction of muscle does not lead necessarily to degeneration of the peripheral neurones.

Archangelsky and Abrikosoff regarded the changes in the cord in their case partly as arrest in development of the grey substance, and partly as a retrograde change. Most muscle-fibres were thin, but their structure was preserved; there was no nuclear proliferation of the muscle-fibres nor overgrowth in the connective tissue, therefore they regarded the muscular condition as arrested development. These findings in the muscles resemble those in the cases of Spiller, Finkelnburg, Lereboullet and Baudouin, and Councilman and Dunn, but Archangelsky and Abrikosoff found diminution in size of the anterior horn-cells, and this finding is like that in the case of Baudouin.

It seems, therefore, that the symptom-complex of amyotonia may depend on purely muscular lesions (Spiller, Lereboullet and Baudouin, Councilman and Dunn), or these muscular lesions may be associated with alteration of the cells of the anterior horns, which in some instances seems to be slight (Lereboullet and Baudouin, Archangelsky and Abrikosoff), in others intense, and when this cellular alteration is intense the distinction from the Werdnig-Hoffman type of atrophy may be difficult.

The Relation of Amyotonia to the Werdnig-Hoffmann Type of Atrophy.

Rothmann [47] has considered this aspect of the subject. Heredity, progression of the disease, reaction of degeneration, and commencement in the proximal parts of the limbs are the most distinguishing features of the Werdnig-Hoffman type. This form has occurred without familial character, as in the cases of Thomson and Bruce, Bruns, Wimmer, Armand-Delille and Boudet. In amyotonia Rothmann believes the spinal process has reached its height at birth, and improvement depends on the condition of the persisting anterior horn-cells. The Werdnig-Hoffmann atrophy, beginning in the second half of the first year or later, has a more gradual destruction of the nerve-cells, and yet Rothmann acknowledges that amyotonia beginning in the first months of life may show much improvement. The improvement in one case, the progression to death in the other are not sufficient to distinguish the two processes. The progression to death may be greatly delayed, as shown in three of Bruns's cases. Rothmann does not regard the reaction of degeneration as an important distinction, and this subject will be considered a little further on in this paper. As for the pathological findings Rothmann thinks they show gradations.

Rothmann's conclusions are :—

Amyotonia in the majority of cases anatomically is a disorder of the anterior horn-cells, and these cells may completely disappear.

All gradations exist between amyotonia and the Werdnig-Hoffmann type, so that sharp distinctions cannot be made between these diseases.

Transitional forms occur between the spinal muscular atrophy of fœtal origin (amyotonia) with affection of the lower cranial nerve-nuclei, and the nuclear loss of Möbius ("Kernschwund") with implication of the spinal cord.

Cassirer [12] regards as important distinctions that amyotonia is not progressive, and the Werdnig-Hoffmann atrophy first is seen in children in the second half of the first year of life. It is questionable whether these can be regarded as important. It is difficult to say exactly when a disease begins, especially when the date of its commencement is often determined by a more or less ignorant parent, and Wimmer's case [58], which he regarded as belonging to the Werdnig-Hoffmann type, was congenital. Cassirer is not willing to class amyotonia under spinal affections, and in his opinion it is closer to myopathy.

The cases of amyotonia with intense alteration of the cells of the anterior horns seem to indicate that the disease may be without amelioration, and even may be progressive. Such cellular changes are usually progressive in spite of all we do to check them.

Batten [4] acknowledges the difficulty in distinguishing between amyotonia congenita and the Werdnig-Hoffmann paralysis. His points of distinction are that in amyotonia a child as a rule can perform all movements in a feeble manner, and there is not the marked degree of flaccid paralysis seen in the case of spinal atrophy. Although hypotonia is present in cases of spinal atrophy, it is not so marked as in cases of amyotonia. The intercostal muscles are commonly paralysed in the spinal atrophy of infants, whereas in amyotonia they are less affected. In brief, in spinal atrophy the paralysis is more marked and the hypotonia less marked than in cases of amyotonia.

It is indeed a question whether further experience will justify these distinctions. They depend upon degree rather than upon quality of characteristics, and do not apply to some of the cases of amyotonia described with intense pathological change of the anterior horn-cells. In a mild case, one in which the spinal changes have not advanced far, and especially one in which the lesions are purely or largely muscular, all movements may be possible.

The flaccidity has been very great in a number of cases of amyotonia, and loss of power has amounted to complete paralysis (Archangelsky and Abrikosoff). In some of the cases of the Werdnig-Hoffmann type the flaccidity has been pronounced, and was so in a case reported recently by Batten and Holmes [8]. These authors had made a diagnosis of the Werdnig-Hoffmann type, but some who had seen the patient had regarded the disease as amyotonia. It is difficult to understand how the intercostal muscles could be little affected when the changes in the anterior horn-cells of some of the cases of amyotonia are so great. One is reminded by these distinctions of the attempt to separate chronic poliomyelitis from progressive spinal muscular atrophy.

The intercostal muscles have been reported as affected in a number of cases of amyotonia. Lugenbühl [42] remarked that the muscles of the thorax and neck were badly developed, and were not active. Pollak [46] said of his case that the thorax and back muscles were paralysed.

In the case reported by Griffith and Spiller [31] there was no history of acute disease. The mother said the boy had never been able to move his legs effectually or to handle objects. He took slight notice of anything, and had never been able to sit up. The legs were motionless and flaccid, the feet in position of foot-drop. The muscles of the legs were soft, but without actual atrophy. The toes and legs could be moved freely by the child when he was stuck with a pin. Passive movement at the knee-joint was unusually free, but there was contracture at the ankle. The muscles of the arms were soft, but not atrophied. The child was able to move the arms very feebly and slowly, and with little ability to handle objects. No tendon reflexes were obtainable. He was unable to sit unsupported, and when held in a sitting position extreme kyphosis developed, and the head dropped in any direction in which gravity acted upon it. When released the trunk would fall in a similar manner, sometimes forward, with the head against the ankles and the arms lying helplessly where they happened to be, and the child was unable to change this position.

Two and a half months after the first observation the intellectual power was found improved, the child took more notice of objects, the power in the upper limbs had increased, and he could now grasp a biscuit and eat it unaided. All movements of the upper limbs were still slow and feeble. There was slight increase of movement in the lower limbs. Under electrical or other stimulation there was decided increase of movement in the limbs, but no distinct muscular contraction was obtained by electricity, faradic or galvanic.

The findings in this case were very similar to those of Rothmann and those seen in the Werdnig-Hoffmann atrophy. I should like to refer to the fact that this child, as in the previous case reported by myself, took little notice of objects, as in no way indicative of poor sight. A child so weak has little interest in what is going on about him.

In the case reported by Gött and Schmidt [27] the clinical picture resembled amyotonia more than the Werdnig-Hoffmann type, except in certain features, viz., the absence of improvement, with a tendency to increase in the symptoms, the presence of reaction of degeneration (this is said to be always absent in amyotonia, but in Thorspecken's case slow reaction was obtained), and the presence of fibrillary tremors (these have never been seen in amyotonia, and are regarded as rare in the Werdnig-Hoffmann atrophy). Opposed to the Werdnig-Hoffmann type were the absence of heredity and familial tendency, and the appearance of symptoms immediately after birth, and not in the course of the second year of life. The findings were those of the Werdnig-Hoffmann type. Gött and Schmidt try to answer those who regard amyotonia and the Werdnig-Hoffmann atrophy as the same disease, but the very case they report is in support of a close relationship between the two. The cases of Wimmer, and Gött and Schmidt show that a congenital form of spinal muscular atrophy exists. The latter case is important, for it had the symptoms of amyotonia, including the hypotonia, and other signs showing clinically implication of the spinal cord. The muscles were much degenerated, the nerve-cells of the anterior horns much diminished in number and size, and the anterior lumbar roots were not so well medullated as the posterior.

Marburg [43] also declines to accept amyotonia as identical with the Werdnig-Hoffmann atrophy. He lays much stress on the absence of the fatty pigmentary degeneration of the nerve-cells in the Werdnig-

Hoffmann atrophy, which is so common in the Aran-Duchenne type, and has never been seen in very early childhood. Since his paper was written, Zatelli [60] has reported the finding of distinct fatty pigmentary degeneration of these nerve-cells, recognized by the Marchi stain, in a case of the Werdnig-Hoffmann atrophy. This seems to be the only case in which this change of nerve-cells has been found in children.

The distinctions Marburg makes are :—

Amyotonia.	*Werdnig-Hoffmann Atrophy.*
Congenital.	Acquired early.
Usually single case.	Usually familial.
General hypotonia.	Localized atrophy, beginning in pelvic girdle.
Atrophy concealed.	Atrophy easily recognizable.
Loss of tendon reflexes.	Tendon reflex activity in proportion to the atrophy.
Electrical irritability (?) or amyotonic reaction (faradic lost, galvanic normal).	Reaction of degeneration.
Improvement.	Progression with constant impairment.

These features, Marburg holds, are the most important, and show the differences between the two diseases. The congenital origin, it has been shown, is not always present in amyotonia, and Wimmer's case of the Werdnig-Hoffmann type and the case of uncertain classification of Gött and Schmidt were congenital. Familial cases are infrequent, but probably occur in amyotonia, and many cases of the Werdnig-Hoffmann type have not been familial. Hypotonia may be pronounced in either affection, although it is likely to be more intense in amyotonia. The atrophy in amyotonia may be distinct, and may implicate the bones, as in the case of Thorspecken. The condition of the tendon reflexes as a point of distinction is unreliable, especially in such young children. Galvanic and faradic reactions were lost in the case of Griffith and Spiller. In Rothmann's case strong faradic irritation gave only slight contraction of the flexors of the forearm, galvanic gave slow contraction, but KClC was greater than the AnClC. This case was studied in Oppenheim's clinic while the child was living, and was accepted as one of amyotonia.

As regards electrical irritability, Cassirer states that the determination of the electrical reactions in amyotonia is difficult in so young children. Some investigators have found that the children endure strong currents easily, but this Cassirer and some others dispute. In no case has a very exact electrical examination been made; according to Cassirer, in general it may be said there is diminution of the irritability, but no qualitative change. A peculiar reaction has been described by Collier and Wilson, and this they call the amyotonic reaction; the muscles react much below normal to a strong faradic current, whereas to the galvanic current the formula and form of contractions are normal. Cassirer says his experience shows that this difference in reaction to the two currents is not present in all cases.

All the muscles and nerves reacted to the faradic and galvanic currents in Thorspecken's case, but to stronger currents and in narcosis. Without narcosis the reactions were uncertain in some of the muscles. Slow reaction to the galvanic current was obtained in two muscles. Oppenheim is said to have had a similar finding in one case of amyotonia.

Improvement is not confined to amyotonia, and in many cases of this disease has not been pronounced, as has already been stated.

It would seem, therefore, that the distinctions given by Marburg are not so positive as they appear at first sight. He regards amyotonia as fœtal acute poliomyelitis, but he acknowledges that the existence of fœtal poliomyelitis has not been positively demonstrated. I do not know of any other writer who has accepted this view. I have seen nothing in the two cases I have studied that would justify such an opinion, and it is disputed by Thorspecken, who distinguishes amyotonia by the great extent and symmetry of the muscular disorder, by the absence of complete loss of function in a single muscle, by the characteristic electrical reaction (of somewhat questionable value), by the absence of vasomotor and trophic disturbances, and by improvement after a period of years.

Batten has attempted to demonstrate that intra-uterine poliomyelitis may exist. The first case reported by him in his paper does not afford absolute proof of fœtal poliomyelitis, but makes it probable. Especially characteristic of poliomyelitis is the elongated patch with almost complete disappearance of medullated fibres in the right ventral horn of the sacral region, represented in fig. 4 of Batten's paper. A patch of this character in the ventral horn, consisting of neuroglia, and without medullated nerve-fibres or nerve-cells, is very suggestive of poliomyelitis. Marburg's view that amyotonia is fœtal poliomyelitis receives some support from Batten's case [5], but in none of the cases of amyotonia have findings exactly like these been described, in none were these characteristic patches of neuroglia tissue representing scar formation following an inflammatory exudate.

THE DISTAL TYPE OF MYOPATHY.

Cases of the distal type of myopathy have been reported by Oppenheim and Cassirer [45], Gowers [28], Dejerine and Thomas [21], Spiller [55], Batten [6], and Cottin and Naville [18]. Campbell's case [10] is somewhat doubtful. To this list I now add another case, although it is without necropsy.

The case of myopathy of the Aran-Duchenne type (the atrophy began in the hands), reported by Merklen and Schaeffer [44] was purely clinical. Reaction of degeneration was present in some muscles of the lower limbs.

In my paper in which a case of the distal type of myopathy was reported, I emphasized the importance of recognizing as belonging to the peroneal (Charcot-Marie-Tooth) type the long-continued and sharp limitation of the atrophy to the parts below the knees and elbows. Cases in which the thighs and upper arms are wasted may belong to this type but they are not questionable.

Batten thinks the disturbance of peripheral sensation, often found in the peroneal type, points strongly in favour of the peroneal type as distinguishing it from the distal type of myopathy, and implication of facial muscles is a point strongly in favour of the muscular origin of the disease.

Hoffmann, however, accepts involvement of the facial muscles as a part of the peroneal type, as Batten mentions, and in Oppenheim and Cassirer's case of myopathy implication of the cranial nerve-supply was slight. In myopathy the atrophy may begin in the distal parts of the limbs, but sooner or later extends beyond them, and the trunkal muscles are likely to be affected. Sensory disturbances are so often absent in the peroneal type that in many cases the condition of sensation affords no means of differential diagnosis.

Cottin and Naville believe that in peripheral myopathy, as regards the hand supply, the atrophy has not the same distribution in the beginning of the disease as in the Aran-Duchenne atrophy. In the peripheral myopathy the hands fall and the fingers are flexed, and atrophy appears later, whereas atrophy is always early in the Aran-Duchenne form, and does not effect the extensors of the thumb and fingers until late. Peripheral myopathy, like the juvenile form, affects especially the extensors. These authors believe that peripheral myopathy begins late (middle life), is not hereditary nor familial, and is more common in females. In my case it began about the age of 26 years, and was in a male. In

Gower's case it began at the age of 10 or 12 years, and was in a male. In myopathic families females are affected later than males, and less severely, or even escape. The frequency of the peripheral myopathy in women affords a contrast to the rarity in women of the Aran-Duchenne and Charcot-Marie-Tooth types of atrophy, in which the distribution and time of onset are much the same. These conclusions of Cottin and Naville are untrustworthy, because they employ three cases only, and ignore those of Gowers, Spiller, and Batten. Gowers's case is referred to as an atypical form. It would seem from the work of Cottin and Naville that in the peripheral type of myopathy the extensors of the hands and fingers and the extensors of the toes are chiefly affected. In Batten's case the patient was a boy aged 3 at the onset of the symptoms. Another case now reported by me is similar in that a young boy was affected.

The boy described by Batten was well until the age of 3, when he contracted measles. A few weeks later the mother noticed dragging of the left leg. Seven months later the right leg became affected, and power in the hands began to be lost at the age of 6. The wasting of the arms and legs progressed slowly. At the time of examination (18 years of age) there was much wasting of all the muscles below the knee and a considerable amount of wasting of the thighs. The foot was in a inverted position, and the boy walked on the outer side. There was marked wasting of all the muscles of the arms below the elbow, and but little power of movement in the hands and forearms. The upper arms and shoulders were well developed. The muscles of the face and trunk were normal. The deep reflexes of the leg were absent. There was no response to faradism or galvanism in any of the muscles below the knee or elbow. Sensation was normal. There was no marked vasomotor disturbance in the legs. Batten, some years previously, had shown this case as one of the peroneal type following measles. At the time of the presentation of this patient he reported the occurrence of the distal type of myopathy in several members of one family. These cases called forth considerable difference of opinion. Holmes remarked that the age of onset of peroneal palsy was higher than in Batten's cases.

A recent case which I have studied is as follows: T. B. (figs. 7 and 8), white, aged 9, came to the Nervous Dispensary of the Hospital of the University of Pennsylvania on June 27, 1911. The first child was born at the sixth month, and died when a few months old. The patient also was born at the sixth month. The labour was normal. He weighed five pounds at birth, was very small, and developed slowly. When he was 3 years old he gradually developed weakness and deformity of the ankles and legs, but there is some doubt whether the weakness began in the ankles or in the thighs; the much greater atrophy of the legs would suggest that the atrophy began in these parts. He was very healthy when 2 years old, and better developed than most children of the same age.

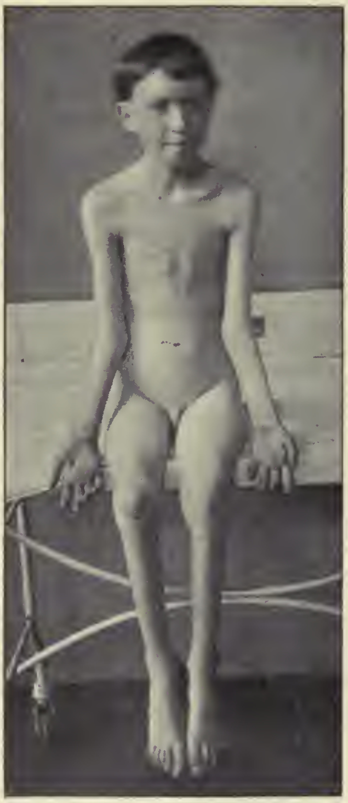


FIG. 7.—Distal type of myopathy. The photograph shows the bilateral foot-drop and greater wasting of the lower limbs below the knees and atrophy of hands and forearms.

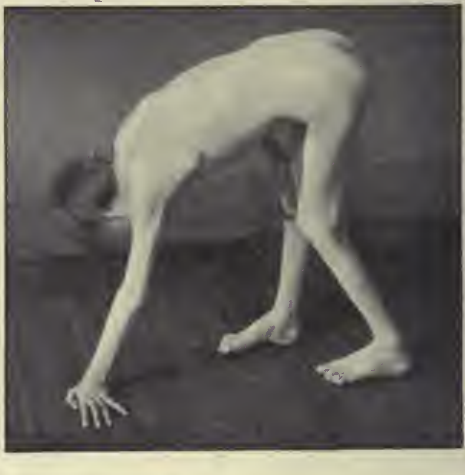


FIG. 8.—Distal type of myopathy. Photograph shows the extent to which the patient was able to rise from the floor. The method of rising is like that of pseudo-hypertrophic muscular paralysis.

In June, 1911, the head was not affected apparently. The movements of the hands were somewhat awkward and ataxic, probably from weakness, and the muscles of the right hand appeared as if they were beginning to atrophy. Both scapulæ were prominent and winged.

The muscles of the back and thorax were small, but there was no localized atrophy in these parts. The feet were placed far apart, and there was grave foot-drop on each side, and steppage gait. When rising from the floor he climbed upon his lower limbs. There was symmetrical atrophy of all the muscles below the knees. The calf muscles seemed stronger than the others. Sensation was normal for pin-prick, but the examination was not satisfactory in this respect. The patellar reflexes were absent and there was no ankle-clonus. The big toes did not move upward in testing for the Babinski reflex. The Wassermann test was negative, the Noguchi positive.

In March, 1912, the atrophy of the small muscles of the hands was pronounced, and much more so than in June, 1911. In raising himself he could not take both hands from the floor.

The boy was examined by me again on December 26, 1912. He was able to walk without support. The lower limbs were weak and the gait was distinctly steppage, because of the bilateral foot-drop. The lower limbs were greatly wasted in all parts, and he was weaker tnan at my last examination. The middle of each leg measured 16 cm. in circumference. He had very little movement in the ankles and none in the toes. The legs were much more wasted than the thighs. The hands were very much wasted, and equally so. The thenar eminence had disappeared, and the hand was of the simian type, with over-extension of the first phalanges of each side. He moved all the fingers freely, but weakly. The forearms were more wasted than the upper arms. The power was greater at the shoulders and elbows than at the wrists. He had no biceps or triceps reflexes. He had winged scapulæ, but not the typical loose shoulders of myopathy. He had no lordosis and no distinct weakness of the thoracic muscles in breathing. The sensation was normal in all the limbs. Galvanic reaction in the muscles of the front of the left thigh and in the right biceps was about normal, although the AnClC was nearly equal to the CClC, but there was not the slightest slowness in the contraction.

The boy had never whistled. He could blow out a lighted match, but he did not pucker up the lips, nor did he seem able to draw up the corners of the mouth—he simply drew the corners a little backward. He closed the eyes, but not with great force, and yet one would hesitate to say that the orbicularis oculi muscles were weak. The face did not appear to be atrophied. The masseter muscles, the tongue and soft palate were normal, and there was no fibrillary twitching of the tongue. Fibrillary twitching was not noticed anywhere.

MYOTONIA ATROPHICA.

Myotonia atrophica is a rare disease in America so far as one may judge from the scarcity of published cases. The recent critical studies of Batten and Gibb, Ascenzi, Hoffmann, and Curschmann have established its position in relation to the myopathies as a distinct form, and differing in important details from Thomsen's disease.

Batten and Gibb [7] mention that in this disease the myotonic features in many cases are very limited in distribution, and occur after the muscular wasting has been present many years. They admit that muscular atrophy may develop in typical cases of Thomsen's disease. The muscular atrophy, they find, has a distribution which is characteristic, and has been present in fifteen out of twenty-seven recorded cases. There is weakness of the face (myopathic face), atrophy of the sterno-mastoids, atrophy of the vasti muscles of the thighs and dorso-flexors of the feet. The masseter and temporal muscles are sometimes affected, as are also the extensors and flexors of the forearm. The disease tends to affect members of a family in the same generation, and is more frequent in the male sex. The distribution of the atrophy in some cases, especially in the legs, bears a resemblance to that of the distal type of myopathy. Chiefly on these considerations Batten and Gibb believe that myotonia atrophica should be regarded as a form of myopathy.

Ascenzi's reason [2] for accepting myotonia atrophica as an entity are: the great frequency of muscular atrophy and myotonia in the same person. More frequently hypertrophy is found with myotonia (athletic type), but muscular atrophy with myotonia affects symmetrical muscles, and has all the characteristics of myopathy. The atrophy probably has often escaped detection until within a few years. Hypertrophy of muscles may be associated with atróphy in the same case. The clinical picture of myotonia atrophica rests on thirty or more cases, and is fairly constant. The pathological findings are similar in myotonia and myopathy. In both males are more frequently affected, in both symmetrical muscles are involved, the proximal muscles are more affected than the distal, the visceral muscles escape, and other signs of involvement of the nervous system are wanting. Ascenzi gives a table of the reported cases. He states that the type described by Batten and Gibb is the most frequent, but irregularities in distribution of the atrophy occur in cases of this type.

The family reported by Greenfield [29] is remarkable in the number of its members affected with myotonia atrophica and early cataract.

In the two cases reported by Kennedy and Oberndorf [39] the first corresponded to the clinical picture of Batten and Gibb. In the second case there was premature bilateral cataract.

Hoffmann [34] says that all the cases of myotonia atrophica in the literature with his own number seventy, at the most eighty. Of these five had hereditary unilateral or bilateral cataract, and three sporadic, i.e., eight altogether, or 10 per cent. Two or three cases are omitted from this list. The percentage of cases in which two so different conditions occurred is so large that a relation of cause and effect must be considered, especially as usually myotonia exists for months or years before cataract develops. If cataract were observed only in sporadic cases of myotonia, it might be supposed to be caused by the myotonia. Against this view is the fact that there are families in which some members have (1) cataract without myotonia, other members (2) myotonia without cataract, and other members (3) myotonia with cataract. The relation of cause and effect therefore can be determined, and both conditions probably depend upon a hereditary diseased anlage of the organism. The lens is from ectodermic tissue, the muscles are from mesodermic. The fact that persons with myotonia atrophica often are psychopaths is to be explained in the same way. Hoffmann says, so far as he knows, cataract has not been observed in the true Thomsen's disease, myotonia congenita without atrophy. This is true also of other forms of muscular atrophy, dystrophy, neuritis (i.e., the Charcot-Marie type), and spinal forms either acute or chronic. He refers to Lange's cases, but makes no further comment on them, and he does not refer to Hamilton's paper [33]. Lange's and Hamilton's cases make his statement as to cataract occurring only with myotonia atrophica inaccurate.

The recent review of myotonia atrophica by Curschmann [20] with a report of six cases of his own, does much to establish the type he designates by the name of Steinert as a distinct disease.

HYPERTROPHIA MUSCULORUM VERA.

The position of hypertrophia musculorum vera (dystrophia muscularis hyperplastica) is still a matter of dispute. Some of the reported cases have shown implication of the peripheral nerves, but the disease on the whole appears to be primarily muscular, and its place seems to be with the myopathies.

Eichhorst [23] in speaking of this type, says Auerbach believes it is only an early stage of pseudo-hypertrophy of the muscles, but against this view is the absence of proliferation of the interstitial connective tissue of the muscles, even when the condition has existed a long time. Eichhorst describes it as a rare disease, concerning the cause of which very little is known.

Talma [56] in 1893 collected the cases belonging to this type in the literature, and reported a case of his own. His patient was about 48, and had the disorder six years. Almost all the voluntary muscles were very large, and although the panniculus adiposus was well developed, the muscles stood out prominently, so that the man could have served for a model of Hercules, and yet he was weak. A piece of biceps muscle removed during life macroscopically appeared to be normal, and there was an increase of fat or connective tissue. On examination sensation was diminished.

The sarcolemmata had disappeared, the primitive bundles were not sharply defined, and they were farther apart than in normal muscles. Many nuclei were found between the primitive bundles, but it could not be determined whether these were proliferated sarcolemma nuclei or whether they had arisen in the interstitial tissue. The transverse striation had in great part disappeared. Spaces containing spindle-shaped cells were found between the fibrils of the primitive bundles. The muscle appeared to be formed by new primitive bundles, and the number of them was increased. Only those which had preserved the transverse striation were supposed to be capable of normal contraction, and the number of these was small. In strict sense it was not therefore a true muscular hypertrophy, as the muscular tissue was not normal. A piece of nerve examined also was not normal.

In a similar case reported by Auerbach the muscles of only one limb were enlarged, sensory disturbances were not present, and improvement occurred after some months. A contraction of this limb was normal at first, but the power soon diminished. In pieces of muscle removed the transverse striation was normal in almost all the primitive bundles. A slight nuclear proliferation was found. Faradic irritability was diminished.

In Berger's three cases only one limb was affected—objective and subjective sensory disturbances were present, and electrical irritability was diminished. In two of these cases only enlargement of primitive bundles was found.

Friedreich described two cases of true hypertrophy of some muscles associated with atrophy of others. In his first case the muscles of the lower limbs were hypertrophied and very hard in voluntary contraction, and their power was increased. The primitive fibres were thick, and their transverse striation in great part normal, and among these were found wax-like degenerated fibres. In his second case, in almost general atrophy, a few muscles were hypertrophied.

In Krau's case some pain occurred, but no changes were found in the nerves. Hypertrophy of muscles was associated with weakness. Pieces of muscles were excised. Most of the fibres had transverse striation, and nuclei were found within the substance of certain muscle-fibres.

Bruch's case was in a child aged 20 months at the time of death. The muscles of the trunk and limbs were thick and hard, and their power was very great. Microscopically the muscles were normal, but thick.

In Pall's case most of the muscles of the body were enlarged and weak. The primitive bundles were found to be normal in an excised piece of muscle.

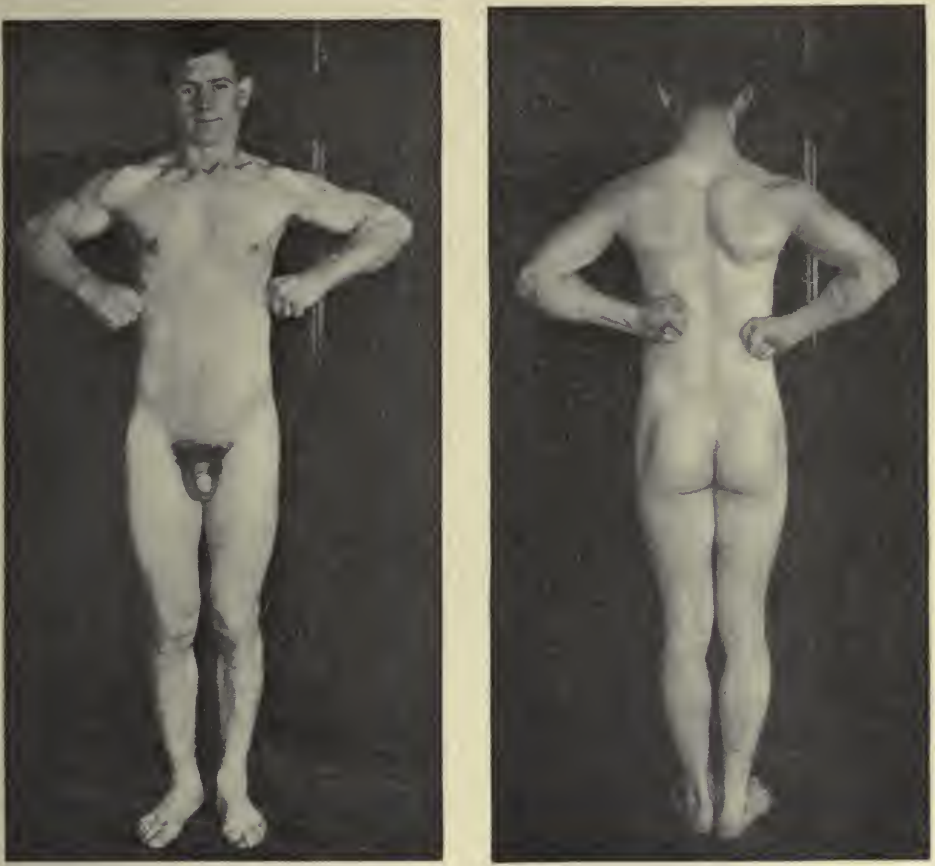
A very interesting case of this excessive muscular development with weakness was observed in our service at the Hospital of the University of Pennsylvania, and was carefully studied and reported by A. H. Woods [59], together with references to the literature. In his summary Woods described the characteristics of the disease as increased bulk of the affected muscles, which feel firm when contracted; diminished power with early fatigue; hypertrophy of individual fibres, some increase in the number of the nuclei; no proliferation of fibrous or fatty tissue, and no degeneration; tendon reflexes, mechanical irritability, and electrical reactions varying from slight diminution to slight increase; no qualitative electrical change; vasomotor changes in a few cases; some dull pain or tenderness of muscles; slow course, with little change from year to year; greater frequency of the disease in males.

In the case reported by Woods, painful muscular cramps occurred, and one of these was seen. A small mass of muscle, 2 to 4 cm. in diameter, rose up, became hard, and formed a rounded tumour, which remained a moment and subsided. Even light tapping of the muscles caused prompt contraction of fibres; in the deltoid and biceps of each side this amounted to a jerk of the whole muscle. These idiomuscular contractions are remarkable, as Babinski and Jarkowski have shown, that while they are absent in myopathy (a fact known previously), they are preserved or exaggerated in neuritis and poliomyelitis. This man was examined in the university gymnasium, and although he was a day-labourer and of unusual muscular development, in muscular power he fell below a man leading a sedentary life, below even the average of 2,000 students, among whom were not merely the young and sedentary, but even some sickly individuals. He fell far below the athletic type of student, with whom he should have compared favourably; the tests being not such as require skill, but those which labourers should best execute.

A piece of muscle was excised from the left triceps and examined. It showed distinct enlargement of fibres in cross-section. The fibres were nearly round in cross-section, the diameters ranging between 70 and 180 microns; most of them falling between 130 and 160 microns; the average being 130 microns. There was no increase in fibrous tissue, endomysium and perimysium being as in normal fibres. There was no sign of fatty overgrowth, and no degeneration of muscular tissue. There was no round cell infiltration.

A typical case of this type has recently come under my observation, for which I am indebted to Dr. W. B. Cadwalader. The patient (figs. 9 and 10) is a man, aged 24. He has six brothers and three sisters, and the brothers appear to the patient to be of unusual muscular development, but without corresponding strength. I have been able to see only one of the brothers, a boy aged 12, who had an attack of poliomyelitis when 19 months old, and has an atrophied right lower limb. He does not appear to be of unusual muscular development. The patient's three sisters are said to be of normal appearance. The man is a plumber, and has done some heavy work. When he was a boy, he says, he was apparently stronger than other boys of his age, but during the past four or five years he has noticed that he is weaker than most men. Four years ago he could carry a bath-tub weighing 280 or 290 lb. upon his back, if some one placed it there, up a flight of stairs. This was difficult to do even at that time, but now it would be impossible. He states that plumbers often carry this weight. He complains of a dull heavy ache in the calves, especially in the morning when he awakens and toward evening. This pain appears to be from use of weak muscles.

When he is stripped he presents the appearance of extraordinary muscular development. His muscles stand out when contracted as do those of a very powerful man. His biceps and deltoid form large masses when the forearms are flexed upon the arms, and the latter are drawn backward. Galvanic reaction is normal in the biceps and deltoid muscles of each side, the KaClC > AnClC, and there is no slowness of contraction. Light touch, pin-prick, moderate degrees of heat and cold are promptly felt in every part of the body. The biceps and triceps reflexes are present on each side, but not very prompt. Either forearm when strongly flexed can be extended by the examiner without much exertion, and with one hand. When either upper limb is held at a right angle with the trunk, it can be depressed by the examiner with slight exertion. There is not the slightest atrophy in any part of the body.



Figs. 9 and 10.—Case of hypertrophia musculorum vera. The muscles are exceedingly well developed, and yet the weakness is very great.

The lower limbs appear well developed, but they are weak. When he attempts to run he almost invariably falls, because of giving way of the lower limbs. He can, however, stand on either lower limb separately. Comparatively little strength on the part of the examiner is required to prevent the man from raising either knee or extending either leg on the thigh. The weakness is noticed especially in climbing stairs. The patellar and Achillis tendon reflexes are about normal on each side.

The man is a Jew. I have been unable to confirm his statement that his brothers are weak, and therefore cannot be certain that the disease is a family one. There can be no doubt that the muscular development is far in excess of the muscular strength. The only sensory symptom is pain, more of a dull ache, although at times it may be more severe; this ache he has always, and has had it since boyhood. I think it is very questionable whether this could be regarded as the result of disease of sensory fibres, and attribute it to constant over-use of weak muscles.

The occurrence of muscular hypertrophy in myotonia atrophica makes the relation of muscular hypertrophy to myopathy more probable. Thus Wardrop Griffith reports a case without necropsy, but with excision of a piece of muscle which presented the symptoms of myotonia in a pronounced form, with marked atrophy of some groups of muscles and an enlargement of those of the calves. In this case there was no increase of the knee-jerks. The histological examination, he says, appears definitely to exclude pseudo-hypertrophic palsy, and to show that there was a real enlargement of the muscular fibres, and that any increase in the general mass of the muscle was not due to fatty or fibrous infiltration. Griffith [30] calls the case one of myotonia atrophica et hypertrophica. The changes in the muscles varied somewhat in the two limbs, upper and lower, but in each instance they were variations in size and in shape of the fibres, and variations in the number and distribution of the nuclei. In diseased muscles the fibres were almost circular in transverse section, and roughly speaking, twice the diameter of those in the control muscle.

A relation of myopathy in some of its types to glandular disturbance possibly may be fully established some day. It is remarkable that in a case of the juvenile type of muscular atrophy reported by J. Michell Clarke [13] there was simultaneous enlargement of the parotid glands. The submaxillary glands were slightly enlarged. This suggests the case of Schönborn, in which all the salivary glands were enlarged, and at the same time there was hypertrophy of all the muscles of the body.

Schönborn [50] thought the case was one of myopathy of toxic nature, possibly from glandular disturbance.

Sacara-Tulbure [48] reported a case of pseudo-hypertrophic paralysis beginning at the age of 48 years, in which she says a remarkable fact was the pronounced development of certain glands, as submaxillary, parotids, axillary, and inguinal. This case was with necropsy.

REFERENCES.

[1] Armand-Delille et Weil, Albert. *Rev. Neurol.*, 1906, t. xiv, p. 190.
[2] Ascenzi. *Monatsschr. f. Psychiat. u. Neurol.*, 1912, Bd. xxxi, S. 201.
[3] Batten. *Quart. Journ. Med.*, 1909-10, vol. iii, p. 313.
[4] *Idem.* *Brain*, 1910-11, vol. xxxiii, p. 433.
[5] *Idem.* *Ibid.*, 1910-11, vol. xxxiii, p. 149.
[6] *Idem.* *Proc. Roy. Soc. Med.*, 1909-10, vol. iii (Neurol. Sect.), p. 92.
[7] Batten and Gibb. *Brain*, 1909, vol. xxxii, p. 187.
[8] Batten and Holmes. *Brain*, 1912, vol. xxxv, p. 38.
[9] Bernhardt. *Neurol. Centralbl.*, 1907, Bd. xxvi, S. 2.
[10] Campbell. *Rev. of Neurol. and Psychiat.*, 1906, vol. iv, p. 192.
[11] Cassirer. Lewandowsky's "Handbuch der Neurologie," Bd. ii, S. 1.
[12] *Idem.* *Ibid.*, Bd. ii, "Specielle Neurologie," Bd. i, S. 230.
[13] Clark. *Brain*, 1903, vol. xxvi, p. 143.
[14] Collier and Wilson. *Brain*, 1908, vol. xxxi, p. 1.
[16] Comby. *Arch. de Méd. des Enf.*, 1906, t. ix, p. 552.
[17] Coombs. *Brit. Med. Journ.*, 1907, vol. i, p. 1414.
[18] Cottin et Naville. *L'Encéphale*, 1912, t. vii, pt. 1, p. 401.
[19] Councilman et Dunn. *Amer. Journ. of Diseases of Children*, 1911, vol. ii, p. 340.
[20] Curschmann. *Deutsche Zeitschr. f. Nervenheilk.*, 1912, Bd. xlv, S. 161.
[21] Dejerine et Thomas. *Rev. Neurol.*, 1904, t. xii, p. 1187.
[22] Duchenne. "De l'Électrisation localisée," third edition, 1872.
[23] Eichhorst. "Handbuch der spez. Pathologie und Therapie innerer Krankheiten," 1907, Bd. iii, S. 932.
[24] Erb. *Münch. med. Wochenschr.*, 1909, Bd. ii, S. 2121.
[25] Eulenburg und Toby Cohn. *Neurol. Centralbl.*, 1911, Bd. xxx, S. 963.
[26] Finkelnburg. *Deutsche Zeitschr. f. Nervenheilk.*, 1908, Bd. xxxv, S. 453.
[27] Gött und Schmidt. *Zeitschr. f. Kinderheilk.*, 1911, Orig. Bd. iii, S. 256.
[28] Gowers. *Brit. Med. Journ.*, 1902, vol. ii, p. 89.
[29] Greenfield. *Rev. of Neurol. and Psychiat.*, 1911, vol. ix, p. 169.
[30] Griffith. *Quart. Journ. Med.*, January, 1911-12, vol. v, p. 229.
[31] Griffith and Spiller. *Amer. Journ. Med. Sci.*, 1911, vol. cxlii, p. 165.
[32] Guillain. *Sem. méd.*, 1907, t. xxvii, p. 277.
[33] Hamilton. *Rev. of Neurol. and Psychiat.*, 1911, vol. ix, p. 645.
[34] Hoffmann. *Arch. f. Ophthal.*, 1912, Bd. lxxxi, S. 512.
[35] Holmes. *Rev. of Neurol. and Psychiat.*, 1908, vol. vi, p. 137.
[36] Holmes, Batten and Barnes. *Proc. Roy. Soc. Med.*, 1908-09, vol. ii (Neurol. Sect.), p. 106.
[37] Howard. *Proc. Roy. Soc. Med.*, 1907-08, vol. i (Path. Sect.), p. 157.
[38] Jendrassik. *Deutsche med. Wochenschr.*, 1909, Bd. xxxv, S. 830.
[39] Kennedy and Oberndorf. *Journ. Amer. Med. Assoc.*, 1911, vol. lvii, p. 1117.
[40] Landouzy et Dejerine. *Rev. de Méd.*, 1886, t. vi, p. 993.
[41] Leclerc. *Gaz. des Hôpitaux*, 1907, t. lxxx, p. 1683.
[42] Lugenbühl. *Deutsche med. Wochenschr.*, 1907, Bd. xxxiii, S. 1439.
[43] Marburg. *Arbeiten a. d. Neurol. Inst. Wien*, 1912, Bd. xix, S. 133.

[44] Merklen et Schaeffer. *Rev. Neurol.*, 1912, t. xxiii, p. 447.

[45] Oppenheim und Cassirer. *Deutsche Zeitschr. f. Nervenheilk.*, 1897, Bd. x, S. 143.

[46] Pollak. *Arch. f. Kinderheilk.*, 1910, Bd. liii, S. 373.

[47] Rothmann. *Monatsschr. f. Psychiat. u. Neurol.*, 1909, Bd. xxv, S. 161.

[48] Sacara-Tulbure. *Rev. de Méd.*, 1894, t. xiv, pp. 273, 494, 992.

[49] Schlivek. *Arch. of Ped.*, 1910, vol. xxvii, p. 34.

[50] Schönborn. *Monatsschr. f. Psychiat. u. Neurol.*, 1910, Bd. xxviii, S. 81.

[51] Sevestre. *Bull. de la Soc. de Péd. de Paris*, February 21, 1899.

[52] Spiller. *Med. Rec.*, New York, 1898, vol. liv, p. 9; "Contributions from the William Pepper Laboratory of Clinical Medicine," No. 1.

[53] *Idem.* *Univ. of Penn. Med. Bull.*, 1904-05, vol. xvii, p. 342; *Neurol. Centralbl.*, 1907, Bd. xxvi, S. 508; Griffith and Spiller, *Amer. Journ. Med. Sci.*, 1911, vol. cxlii, p. 165.

[54] *Idem.* *Journ. of Nerv. and Ment. Dis.*, 1907, vol. xxxiv, p. 14.

[55] *Idem.* "Contributions from the William Pepper Laboratory of Clinical Medicine," 1900.

[56] Talma. *Deutsche Zeitschr. f. Nervenheilk.*, 1892, Bd. ii, S. 197 (literature to the date of this paper given by him).

[57] Thorspecken. *Jahrb. f. Kinderheilk.*, 1912, Bd. lxxvi, S. 300.

[58] Wimmer. *Arch. f Psychiat.*, 1907, Bd. xlii, S. 960.

[59] Woods. *Journ. of Nerv. and Ment. Dis.*, 1911, vol. xxxviii, p. 532.

[60] Zatelli. *Arbeiten a. d. Neurol. Inst. Wien*, 1912, Bd. xix, S. 436.

PUBLICATIONS RECENTLY RECEIVED.

[Notes on a book under this heading do not preclude a subsequent review.]

Vitalfärbung am Zentralnervensystem. Beitrag zur Physio-pathologie des Plexus Choroideus und der Hirnhäute. Von Prof. Dr. EDWIN E. GOLDMANN. S. 60, mit 4 Tafeln. Berlin: Verlag d. K. Akad. d. Wissenschft. 1913.

This work has become of pathetic interest from the untimely death of its author. In his researches on serous membranes and their functions in inflammation, he had been led to lay stress on the presence of certain large granular cells, "pyrrhol" cells, and therefore examined the reactions of the central nervous system to trypan- and isamin-blue. If the staining material is injected into the blood the choroid plexuses are stained, but the entire nervous system remains free from colouring matter. Thus he believed that the cells of the choroid plexus guard the central nervous system from the action of noxious materials circulating in the blood. When, however, the blue stain is injected into the cerebrospinal fluid the whole of the spinal cord, brain-stem, and optic nerves are deeply stained, and on microscopical section the ganglion-cells in particular are seen to have absorbed the intra-vital coloration. The cerebellum, cerebrum and nerve-roots escape. If the stain is injected into the cerebral subarachnoid space, the colouring material then attacks the cerebral hemispheres.

The author holds that the cerebrospinal fluid carries on the nutritive and excretory functions of the central nervous system, and that the whole of this circulation is guarded by the cells of the choroid plexuses from direct continuity with the blood-stream. In inflammation of the meninges these conditions are changed, and the cerebrospinal fluid and nervous system may be flooded with abnormal substances. Directly the membranes are inflamed the "pyrrhol" cells appear in great numbers and act as phagocytes to the central nervous system.

Zur Psychopathologie des Alltagslebens. Von Prof. Dr. SIGM. FREUD. Vierte, vermehrte Auflage. S. 198. Berlin: Karger, 1912.

This is a new edition of Freud's work in which he explains the acts of forgetting, of saying, reading or writing the wrong word, or of choosing the wrong object by normal human beings. Underneath each wrongly performed act lies an interfering complex. The one common character which underlies all such acts is the repercussion of incompletely suppressed psychical processes which, although not consciously active, have not lost all power to express themselves on the activities of consciousness. A multitude of examples is cited for everyday experience and from European literature.

Papers on Psychoanalysis. By ERNEST JONES, M.D., M.R.C.P. Pp. 432. London: Baillière, Tindall and Cox, 1913.

This selection from the author's papers is arranged to follow the main lines of Freud's psychology; but although it begins with an excellent short account of Freud's views, it is occupied mainly with personal experiences of normal and abnormal mental phenomena. Dr. Jones deals with the psychopathology of everyday life, the pathology of morbid anxiety, psychoanalysis in its various forms, amnesia, dreams, and with most of the questions that have been opened up by the work of Freud. The book is extremely well written, and can be strongly recommended to those who wish to gain knowledge of this movement in psychology from the point of view of an ardent disciple.

Der Kopfschmerz. Von Dr. SIEGMUND AUERBACH. S. 132. Berlin: Springer, 1912.

The headaches of primary origin are divided into three groups: migraine, the neurasthenic, and the so-called rheumatic headache. Under migraine the author, like most Continental authorities, includes many periodic and bilateral forms of pain in the head which do not correspond strictly with what is called migraine in this country; for here migraine is usually employed for a form of headache mostly unilateral, and frequently accompanied by fortification-figures, hemianopsia, or other visual phenomena of a high order. The neurasthenic or "fatigue" headache is described, and he then passes on to a form of pain in the head which is scarcely recognized in this country. This is the "rheumatic" ("Knötchen") headache characterized by small thickenings in the connective tissue of the scalp and fascia covering the muscles of the head and neck. The treatment to be employed in such cases is described, and several illustrative clinical histories are given in full. The author then passes to those headaches produced by disease of internal organs; this is the weakest part of the book. He closes with a description of headache in infectious and constitutional diseases.

Lectures on Clinical Psychiatry. By Professor EMIL KRAEPELIN. Authorized Translation from the Second German Edition. Revised and edited by THOMAS JOHNSTONE, M.D. Third English Edition. Pp. 368. London: Baillière, Tindall and Cox, 1913.

These are essentially practical clinical demonstrations starting from a given patient, and developing the theme with the help of other examples of the same disease. The lectures on dementia præcox and katatonia are particularly valuable, whilst every chapter contains many points of interest. The book is preceded by a tabular statement of Kraepelin's Classification of the psychoses. The translation is excellent.

Mind and its Disorders: A Text-book for Students and Practitioners. By W. H. B. STODDART, M.D. Second Edition with illustrations. Pp. 518. London: Lewis, 1912.

This excellent text-book has been brought up to date, and every chapter shows more or less extensive changes and improvements. It can be strongly recommended to students anxious to obtain a knowledge of the physical aspects of mental disease.

Eléments de Sémiologie et Clinique Mentales. Pàr le Dr. Ph. CHASLIN. Pp. 956. Paris: Asselin et Houzean, 1912.

This text-book is based on the clinical manifestations of insanity, arranged partly under the cause, such as alcohol or organic disease, and partly under such headings as "Folies de persécution," "Folies discordantes," &c. To English readers, interested in the present state of psychiatry, this book will afford many points of comparison with similar works in English and German. The author gives an interesting account from personal experience, of the progress of views on hysteria in Paris from Charcot to the modern school.

Writers of "Original Articles and Clinical Cases" are supplied free of charge with 50 copies reprinted in the form in which the paper stands in the pages of "Brain." If reprints are required in pamphlet form, with wrapper, title-page, &c., and re-numbered pages, they must be ordered, at the expense of the writers, from Messrs. BALE, SONS & DANIELSSON, Ltd., 83-91, Great Titchfield Street, London, W.

Members of the Neurological Section of the Royal Society of Medicine can obtain the Index of "Brain" for the Volumes I. to XXIII. inclusive, that is, from its commencement to the end of 1900, from Messrs. MACMILLAN & CO., Ltd., St. Martin's Street, London, W.C., at the price of 6s. 6d., post free.

To those who are not members of the Neurological Section of the Royal Society of Medicine the price is 8s. 6d. net, and the volume may be obtained through any bookseller.

EDITOR.

[NOVEMBER, 1913.]

BRAIN.

PART II., VOL. 36.

EXPERIMENTAL AND PATHOLOGICO-ANATOMICAL RESEARCHES ON THE CORPUS CALLOSUM.[1]

BY DR. C. T. VAN VALKENBURG, AMSTERDAM.

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INTRODUCTION.

ON separating the two fore-brain hemispheres of any mammal, the corpus callosum becomes visible; its position between the two halves of the brain at once suggests that it serves as a connecting link between the hemispheres.

There is no doubt that certain bundles exist in this mass of fibres, the origin and termination of which lie on the same side of the middle line. These are the fibres which belong, in the wide sense of the term, to the olfactory system, i.e., the fornix longus, tænia tecta, and the nervi Lancisii. These fall outside the province of this research, which is confined to what is commonly understood as the corpus callosum, that is to say, the chief interhemispherical commissure of the neopallia.

The term commissure may either be understood to mean a connexion of corresponding regions of the opposite hemispheres; or, taking it in a broader sense, a connexion in general of the one half of the brain with the other, through which both homotopical and heterotopical cortical regions are associated with each other. To give the word its full meaning it connotes an interhemispherical association system.

Both interpretations are found in the literature, though it is not possible to state that they always rest upon conclusive anatomical or pathological evidence. The more modern writers embrace the latter opinion on the whole, chiefly on the strength of Cajal's histological investigations; in small mammals, as the mouse, with the aid of his silver methods, Cajal found that from cortical cells axones arise, which either directly or as collaterals of projection and longer association neurons, pass to homo- and heterotopical points of the opposite hemisphere through the corpus callosum [4].

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[1] Dedicated to Professor von Monakow.

I believe that this conclusion concerning the ending of the callosal fibres cannot be positively proved from normal silver preparations. Moreover, were normal histological investigations sufficient to place Cajal's theory beyond all question, they afford very little evidence of the "associative" nature of the commissure. Cajal believes that the callosal fibres give off collaterals before ending, but these can be followed with certainty over very insignificant distances only in one section. Though strictly speaking the term association may be applicable to such a connexion, it approaches more nearly to what one may consider as a commissure. In any case it is evident that Cajal's theories, although they may be perfectly correct, by no means justify the frequent assumption that heterotopical cortex regions of both hemispheres stand in connexion by callosal fibres with each other (Ascenzi [2] and others).

In addition to Cajal's and Kölliker's [20] histological results certain morphological investigations support this view. Dejerine cites Schnopfhagen's [44] investigations in proof of heterotopical connexions, but it need hardly be said that the antiquated and highly uncertain "Abfaserung" methods of this writer cannot assist in the solution of the point at issue.

Other methods that have been employed to solve this problem may be briefly considered.

(1) *Teratological cases.*—Agenesis of the corpus callosum has afforded little information on the normal course of the callosal fibres. In the first place there are generally other developmental disturbances in the brain which make it very difficult to arrive at definite conclusions; and when no other disturbances are present, the difficulty remains as to whether the corpus callosum was actually absent, or whether it had not reached the opposite hemisphere. This question is closely connected with the significance of the so-called "Balkenlängsbundel" (Probst [40]). As regards the extensive literature on this subject, I refer for instance to Marchand [29]. The latest contributions to the subject, those of Stöcker [48] and Landsbergen [22], are of no assistance in the solution of our problem.

(2) *Embryology.*—Neither the study of the primary development of the commissural system (His [16], Zuckerkandl [58, 59], Goldstein

[12], Langelaan [23], and others), nor of the myelogenesis of the corpus callosum, have thrown more light on the origin and termination of the commissural fibres.

(3) *Secondary fibre-degeneration.*—The early investigations of Forel [9], v. Gudden [49], and v. Monakow [50] showed that after extensive lesions of one hemisphere, degeneration ensued in the corpus callosum, which could not be followed by v. Gudden's method, nor, as Sherrington [47] and Langley and Grünbaum [24] found, by the method of Marchi, to the cortex of the opposite side. Experimental section of the corpus callosum also threw no light on the course of the fibres. (Muratoff [36], Lo Monaco e Baldi [34], Levy-Valensi [26].) Lo Monaco e Baldi's conclusions chiefly concern the question as to whether the tapetum of the posterior horn in the cat belongs to the corpus callosum. Muratoff concluded that heterotopical connexions are present in the corpus callosum in the dog. Lévy-Valensi agrees with this statement; without, as far as I can see, giving reasonable grounds in support of it.

It is generally accepted that extensive unilateral cortical lesions in the human brain cause atrophy of the corpus callosum, which is practically parallel with the extent of the destruction of the cortex, but Kattwinkel's [18] conclusions are at variance with this. Presumably the cause lies in the final complete disappearance of the degenerated callosal fibres. Exact details concerning the areas of the cortex of the opposite side, which are reached by the degenerated fibres, are, however, rare. It is unnecessary to discuss the views which have been put forward by different authors. According to Anton u. Zingerle [1] a considerable fibre radiation from the frontal lobe of the one hemisphere attains the distal part of the cortex of the opposite side. Probst [41] makes a similar statement. Dejerine's [6] detailed analysis of the callosal fibres and their relation to certain cortical regions is based on cases in which the degeneration of the corpus callosum was probably primary, and is therefore not wholly convincing. On the other hand, one finds of late only one positive assertion that the corpus callosum unites homotopical regions only of both hemispheres (Niessl von Mayendorf [38]), and that is based on the study of degeneration preparations. Similarly, the numerous cases of primary lesions in the corpus callosum have, so far, not contributed to a better knowledge of the manner in which the hemispheres are connected with each other. (Ransom [42], Mingazzini [31], Marie et Guillain [30], Gianelli [11], Ascenzi [2], and others.)

The question as to which cells of the cortex the callosal fibres pass, is briefly considered by Dotto and Pusateri [7]; they place them, from the examination of Marchi preparations, in the third layer, but what these writers mean by the third layer is not certain, and they give no illustration of their preparations.

Lévy-Valensi, after section of the corpus callosum, could trace the degeneration into the layer of the "large pyramids" but not into that of the lesser pyramids. It is not apparent what he desires to convey.

I know of no degeneration investigations on the human brain which have led to any positive result.

(4) *Retrograde cell degeneration* (axonal reaction).—This method has been little employed, either after experimental section of the corpus callosum, or morbid lesions therein, to determine whether cells of any definite region or character show a reaction. Observations on the cortical cells in cases of agenesis of the corpus callosum permit no conclusions. I will discuss later my own findings on the rabbit and cat, and those of de Vries on the mouse.

Thus, our exact knowledge of the interhemispherical callosal fibres is less than one might suppose.

Whether the commissure connects homotopical or heterotopical regions is so far uncertain; from what cells its fibres arise, and about which cells they end is also undetermined. And even the statement that all brain convolutions, except the olfactory region, are connected by the means of the corpus callosum, is open to question. Indeed, in 1891 Beevor [3], in a very careful anatomical study, found that the calcarine cortex of the marmoset monkey is not connected by a commissure with the opposite side. In later publications this theory, if mentioned at all, is considered absurd, but actual proof of its inaccuracy is nowhere to be found.

Equally little of importance is known of the manner in which a possible heterotopical commissure unites the two brain hemispheres. And yet in view of certain clinical and experimental observations of recent years, it is of the highest importance that we should have better information on this matter. I refer here to two groups of clinico-pathological and experimental investigations, namely, Liepmann's [27] study of apraxia callosa, and the effects of section or stimulation of the corpus callosum.

A number of cases have already been published by Hartmann [14], Liepmann u. Maas [28], v. Vleuten [56], Goldstein [13], and others, in which apraxia of the left extremities was probably a result of a lesion of the connexion of the right hemisphere with the left. The accepted explanation of these motor disturbances was interruption of the connexions between both sensorio-motor zones, in the sense of Heilbronner and Liepmann.

It is remarkable that in not a single case, even when the brain was examined in serial sections, was any light thrown upon the course of this supposed connexion. It need hardly be pointed out that not until we have a better and more accurate knowledge of this connexion shall we be in a position to understand the anatomical basis of apraxia.

Mott's [35] excitation experiments, which seem to indicate that the anterior callosal fibres are in relation to certain parts of the musculature of the body, were put forward by this author as evidence of the existence of a connexion between the motor cortical regions and the giganto-pyramidal cells they contain. Later, neither Korányi [21], Lo Monaco [33], nor Lévy-Valensi could with certainty, even when employing very strong currents, confirm Mott's observations on the dog and monkey. Stimulation in their hands produced no motor effect, and section, as Carville et Duret [5], Muratoff [36], Sherrington [47] and others found, no permanent results.

The explanation of the effect of section of the corpus callosum on the hemianopsia, which occurs for a time in dogs after lesion of the occipital lobe, is equally uncertain. In this respect Korányi's [21] results differ from those of Yoshimura [19].

In each case it seems desirable to control as far as possible the positive or negative results of physiological experiments by recognized anatomical facts. This shall be the aim of my investigation.

Experiments on mice, rabbits, cats, were made in order to trace the origin and the ending of the callosal fibres. Pathological human cases supplied material for the study of the more accurate anatomy of the callosal radiation. The localization of these pathological lesions revealed important details in respect to two regions of the cerebral cortex, the Rolandic zone and the visual sphere. The fact that these two regions are of primary clinical and physiological importance, is ample inducement for the communication of my observations and the reproduction of some preparations.

Experimental Observations.

Different lengths of the corpus callosum were divided sagittally in a number of mice, rabbits and cats, in order to determine from which cell layers of the cerebral cortex callosal fibres arise, and to demonstrate in which layer of the cortex they end. The result of these investigations has been already published in part [54, 57]. This communication will be referred to for minor details, but the facts obtained by operation on rabbits and cats are here repeated; the changes found in the mouse do not differ essentially from those in the rabbit.

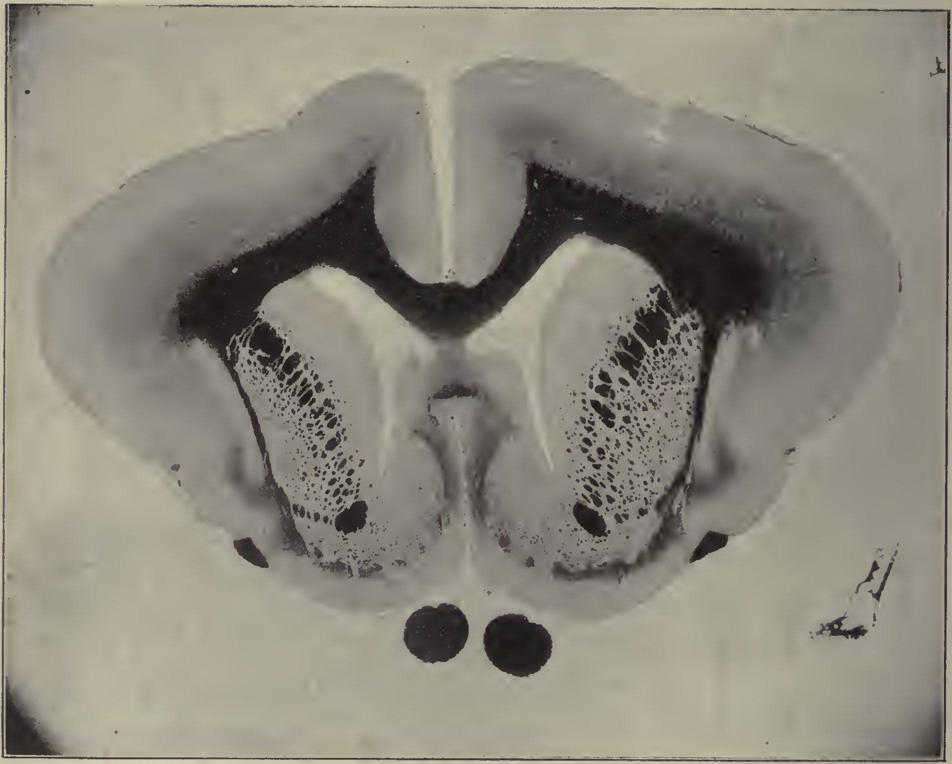

FIG. 1.—Rabbit: normal.

Rabbit.

The section was made either in the median line between the two hemispheres, or close to it. Nissl's and Weigert-Pal's methods were employed in the investigation. For cell changes, that hemisphere in particular was examined which was not injured by the operative lesion.

The corpus callosum was divided either by incising the dorsal surface of the pallium and the white matter, including the corpus callosum beneath it; or a sickle-shaped knife was inserted through the corpus callosum into the lateral ventricle, and then drawn backwards and forwards through its entire length. This operation causes no other disturbance if the knife is, as far as possible, taken out in exactly the same place as it was inserted. The consequences of such a section is shown in fig. 2. It will be seen that the fibres of the internal capsule and corpus callosum are cut through in the dorso-median part of the right hemisphere.

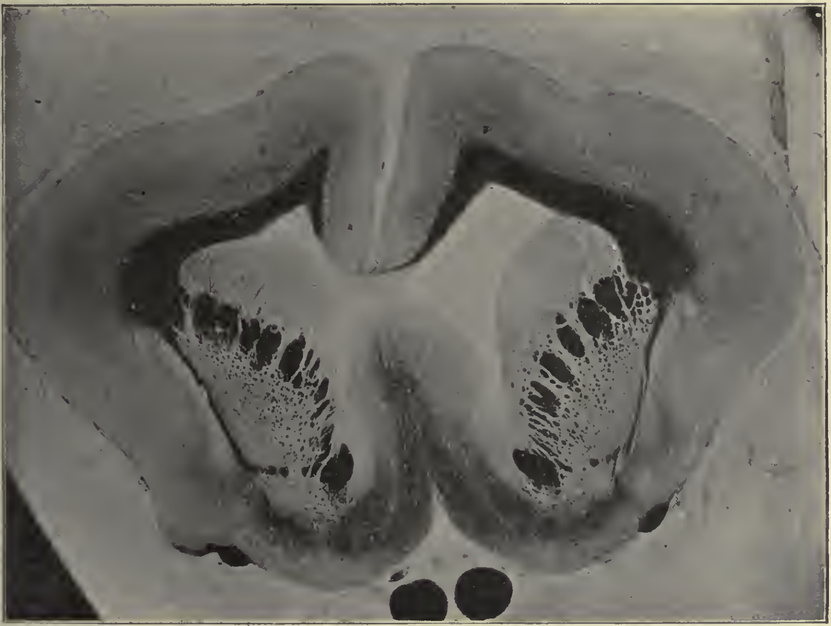

Fig. 2.—Rabbit: section of the corpus callosum in the left hemisphere.

On comparing fig. 2 with a photograph of a normal section at the same level (fig. 1), the smaller bulk of the centrum ovale in the left hemisphere is evident. The part which normally borders the ventricle medio-dorsally and laterally, has disappeared, except a small remnant, which is the fasciculus subcallosus. In the lateral direction the white matter increases rapidly in bulk; this shows that the callosal fibres, shortly after having crossed the median line, pass through the centrum ovale to the cortex. There is no area of degeneration in the central white matter; evidently the normal myelinated fibres come together as the degenerated fibres disappear. I may add that Marchi preparations from other rabbits operated on in the same way, led to the same result as regards the course of the fibres. The degeneration shown up

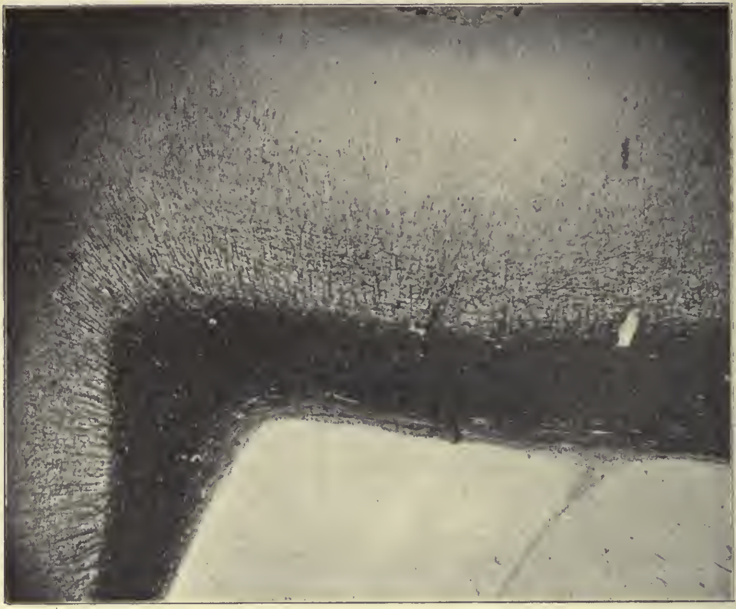

FIG. 3.—Rabbit: division of the corpus callosum in the left hemisphere. Right half of fig. 2; more strongly magnified.

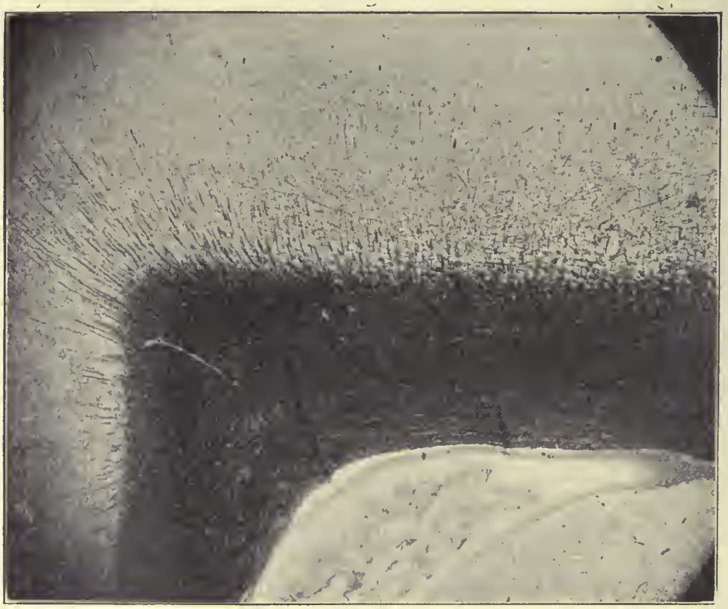

FIG. 4.—Rabbit: normal. Right half of fig. 1.

by this method was, however, unsatisfactory, but it was not in conflict with the observations made on Pal preparations. As the affected callosal fibres must have degenerated to their terminations, one must seek for the evidence of this in the cortex. This is, however, more difficult to find than one would suppose a priori. Indeed, the reader, on comparing the more strongly magnified figs. 3 with 4, without a magnifying glass, will hardly succeed in detecting any difference between the normal cortex and that of the uninjured side in the operated animals. But on closer scrutiny a loss of fibres may be seen in the medio-dorsal cortex in fig. 3. This lies in the regio præcentralis, the area giganto-pyramidalis or field 4 of Brodmann.[1]

The loss affects the radiary fibres in the dorso-median part of the central white matter. There is a diffuse diminution of these fibres, in fact, the somewhat longer ones have entirely disappeared, so that the numerous shorter fibres appear to be unduly separated from each other, but it is not possible to show that these have decreased in number. It is difficult to say to which layer the longer cortical radiations that have disappeared, normally penetrate, because in the area giganto-pyramidalis of the rabbit, the boundaries of the layers are indistinct; the actual "giganto-pyramids" of layer V extend among the pyramidal cells of the more superficial layers, while, as in all animals, the lamina granularis interna is absent. In any case the longest radiating fibres in the normal cortex only penetrate half its depth. These have disappeared in the operated rabbit.

There is also a loss of fibres in the regio post-centralis (field 1 + 3 of Brodmann). In this region, in the normal rabbit, the peculiar comparatively deeply penetrating cortical rays of field 4 do not occur, but short fibres which do not penetrate beyond layer VI, or V, are present in great number; they are moderately thick. Moreover, many fibres coming from the central white matter are cut transversely in frontal sections close to the centrum ovale. Several of these short radiary rays and transverse straight fibres have also disappeared in the uninjured hemisphere. The tangential network of fibres appears to be perfectly intact. The fibre decrease in the cortex of this region is greatest on the dorsal side, and is no longer recognizable on the lateral surface of the hemisphere. The dorso-median part of the normal cortex of this region has no long radiary fibres.

The rest of the dorso-lateral part of the hemisphere is also less rich in coarse fibres than this region in more frontally situated sections. On comparing the uninjured hemisphere of the operated rabbit with the normal, a slight though distinct diminution of these coarse fibres in the inner part of the cortex is apparent.

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[1] Plate VII from Winkler and Potter: "An Anatomical Guide to Experimental Researches on the Rabbit's Brain," Amsterdam, 1911, may serve for comparison.

Further laterally the loss of fibres is of the same character as that described in field 1 + 3.

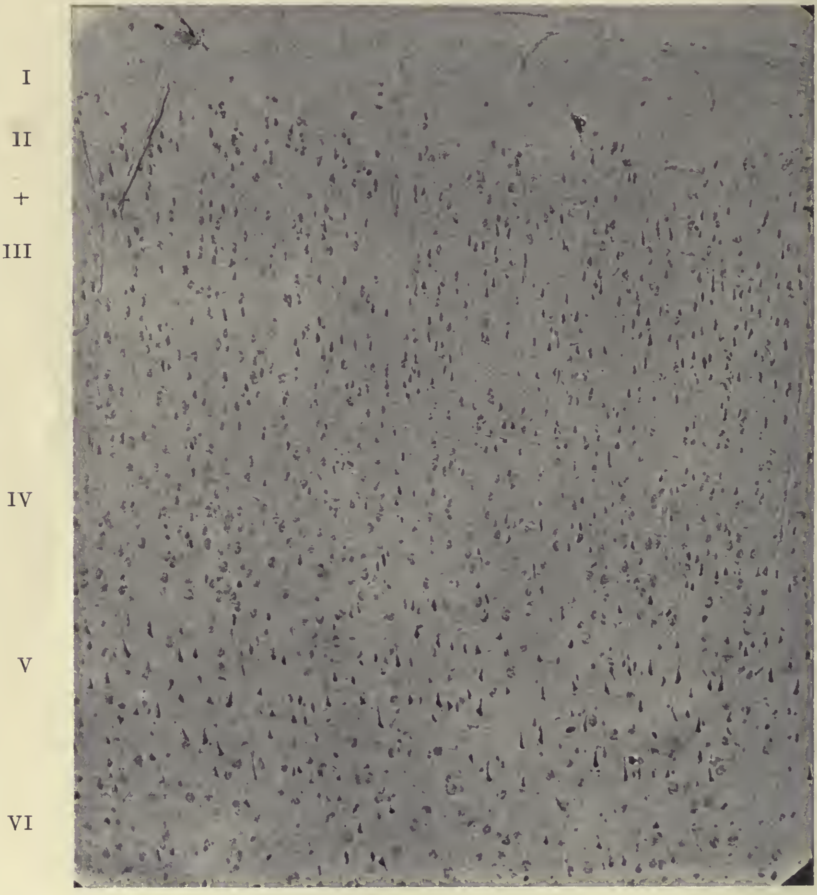

Fig. 5.—Rabbit: normal. Field 1 + 3 (Brodmann). Toluidin blue.

On further comparing preparations from the further occipitalward parts of the cortex of the operated and non-operated animals with each other, the differences are difficult to determine, and it is impossible to show them in a photographic reproduction. Behind the splenium, even microscopic examination cannot detect any perceptible difference.

In order to trace the origin of these fibres, operations were performed in the manner described above and the uninjured hemisphere was examined by Nissl's staining after paraffin imbedding.

It is extremely important to compare the cortex of a rabbit in which cell degeneration is suspected, with a normal series which has been treated in exactly the same way, as the appearance of the cells depends to a great extent upon the manner in which the sections are stained with the toluidin-blue solution. The same cells may appear dark blue and homogeneously coloured in one preparation, and in another pale blue, with only scanty loose protoplasm. It is therefore very easy to mistake degenerations for what is normal. On the other hand, one is very liable, in the cortex of the rabbit, to overlook cell

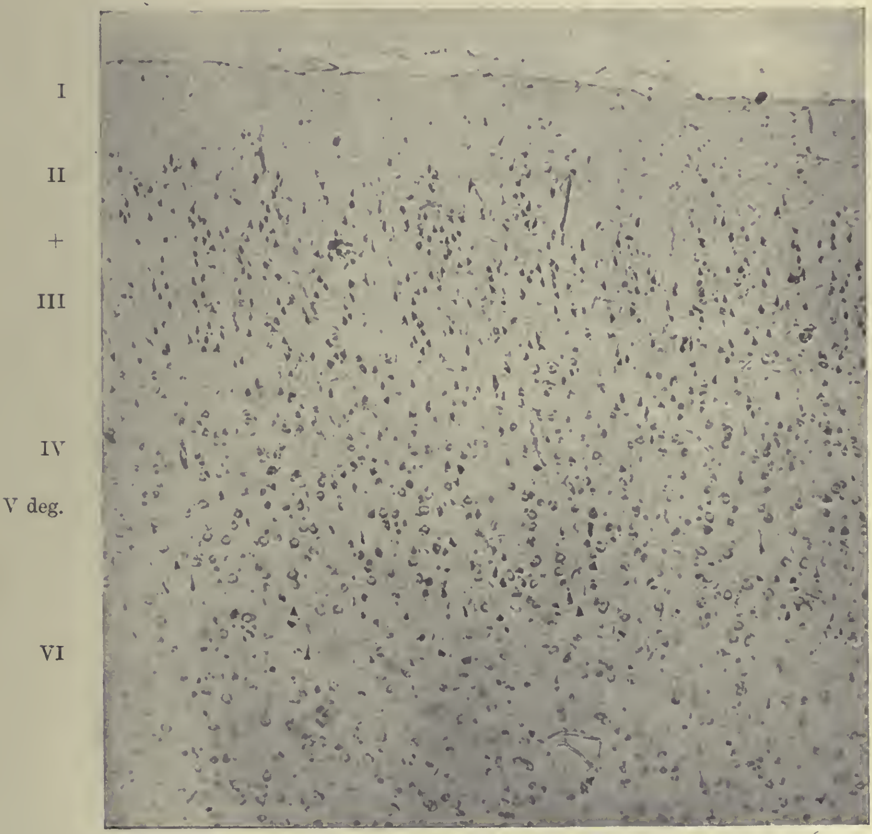

Fig. 6.—Rabbit: divisions of corpus callosum. Field 1 + 3 (Brodmann). Toluidin blue.

changes which actually exist; even in regions where fibre preparations show they must exist, often not a trace of them can be found. I have been able to detect them with positive certainty only in Brodmann's fields 4, 1 + 3, 5 + 7. I am unable to illustrate these changes in the area giganto-pyramidalis distinctly in a photograph. De Vries [55] was successful in the mouse, but the alterations in the other fields in this animal were far more distinct.

Fig. 5 shows a transverse section through field 1 + 3 of a normal rabbit, and fig. 6 is from the homologous area of the uninjured hemisphere of a rabbit in which the corpus callosum was cut. There is a distinct pallor in the staining of the large pyramids in layer V (subgranular), and at the same time an apparent decrease of the smaller cells of layer VI, but this is less distinctly visible. The more superficial pyramidal cells (supragranular) are equally developed in both. There is no distinct proliferation of the neuroglia.

These illustrations have been taken from an animal which lived seventy days after the operation; experience teaches that the cell changes show up most clearly about that time. If the animals are allowed to remain alive for one or two years it is extremely difficult to detect any changes; and changes may be visible two or three weeks after the operation. I did not operate on newly born rabbits; according to Nissl [39] callosal lesions, in these animals, produce no appreciable changes, but it seems doubtful if this is correct.

From the experiments upon the rabbit, which are fully confirmed by those on the mouse, the following conclusions may be drawn:—

As far as can be determined the origin of the callosal fibres lies in the subgranular layers of the cortex, and apparently exclusively in that of fields 4, 1 + 3, 5 + 7. In any case there is no reason to suppose any callosal fibres spring from more distant fields. Callosal fibres end in the same regions; the radiation containing callosal fibres in field 4 ascends higher into the cortex than in the remaining fields, in which it does not pass the lamina granularis interna; but it is, of course, possible that they may penetrate higher into the cortex after losing their myeline sheaths.

Whether the callosal connexion is homotopical or heterotopical could not be determined with certainty. Partial cortical lesions of one hemisphere produced, as a rule, only a doubtful cell affection of the cortex on the opposite side, but when a reaction was observed, it was at any rate homotopical. Fig. 7 is from the same cortical area as the former figures (field 1 + 3); the corresponding point of the contralateral hemisphere was extirpated, and it will be observed that there is a moderate decrease of deeply coloured cells in layer V. In the cat a complete sagittal division of the corpus callosum is not possible without considerable injury of the brain. Partial section is, however, possible, and in different experiments all parts of it were cut.

In these investigations the methods of Weigert-Pal with Van Gieson, or of Nissl were employed: the first to trace the secondary degeneration of the fibres, the second in order to demonstrate the reaction in their cells of origin. Marchi's method was of little service; it is certainly inferior to Pal's staining in showing up degenerating or degenerated callosal fibres.

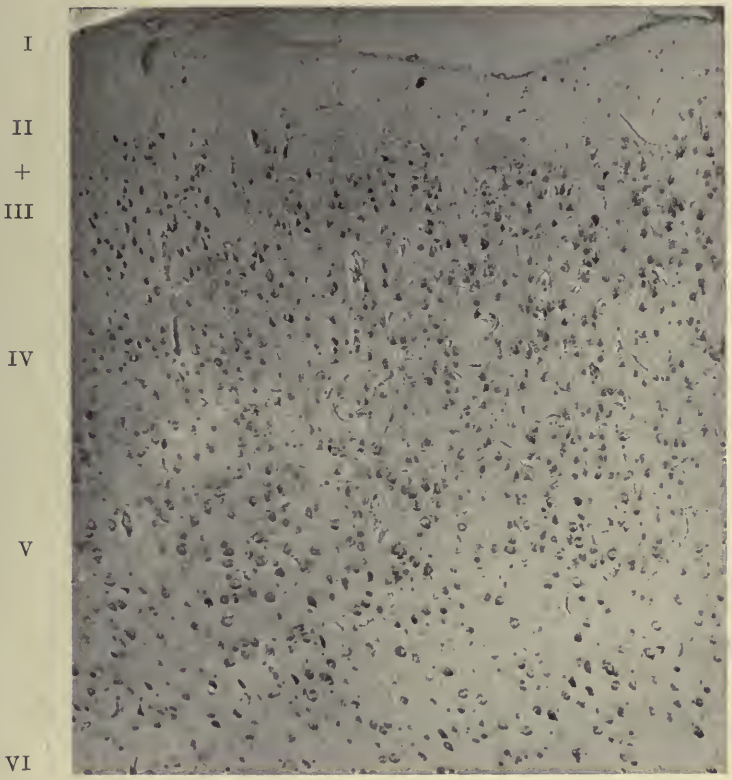

FIG. 7.—Rabbit. Extirpation of field 1 + 3 (Brodmann) in the left hemisphere. Field 1 + 3, right hemisphere. Toluidin blue.

Examination by Marchi's method after section of the frontal part of the corpus callosum gave, as Sherrington has found, more or less insignificant results. After division of its posterior half, both Pal's and Nissl's methods could be employed with more success.

I will not enter on the much discussed question whether the tapetum ventriculi consists of fibres of the corpus callosum. My results agree on the whole with those of Muratoff and others; the fibre-layer lying immediately above the occipital part of the ventricle consists of thin fibres palely stained by hæmatoxylin (fasciculus subcallosus, Muratoff), which possibly stand in connexion with the nucleus caudatus and the subependymal grey matter. They degenerate partially on the side of the lesion particularly when the nucleus caudatus is injured, and they remain intact on the uninjured side. Close to the median line all the callosal fibres degenerate; further lateralwards the degeneration is most distinct where they bend round the lateral angle of the lateral ventricle. It is impossible to discover well-defined degeneration in the centrum ovale. Peripherally from it, at the base of the gyrus ectolateralis, there is a loss of fibres which can be followed up to the cortex.

In the gyrus ectolateralis immediately anterior to the area striata, the subcortical white matter is less coloured than in the corresponding area of the normal animal. In the cortex itself the long, radiating fibres are greatly diminished in number. In the more posterior part of the cortex this degeneration is found only in the gyrus ectolateralis. Further frontally, a similar fibre diminution may be observed in the bend of the gyrus suprasylvius, which borders the gyrus ectolateralis. Frontal to the lesion of the corpus callosum, there is no degeneration, but I possess only Marchi preparations of this region after callosal lesions. The course taken by the degenerated cortico-petal fibres is illustrated by Sherrington and others; they spread in smaller numbers than one would expect, from the degenerated corpus callosum into the centrum ovale and can be traced right into the base of the lateral and dorsal gyri, but apparently only few extend in front of the sulcus cruciatus.

Only a few black granules can be seen in the deeper layers of the cortex; there is no question of being able to follow a typical Marchi degeneration of the radiary fibres high up into it. Portions of the cortex behind the operated region are entirely free from secondary degeneration.

Nissl preparations of cats operated upon in the above described manner show the following changes:—

Cell changes are found exclusively in those convolutions of the uninjured hemisphere, in which secondary fibre degeneration was

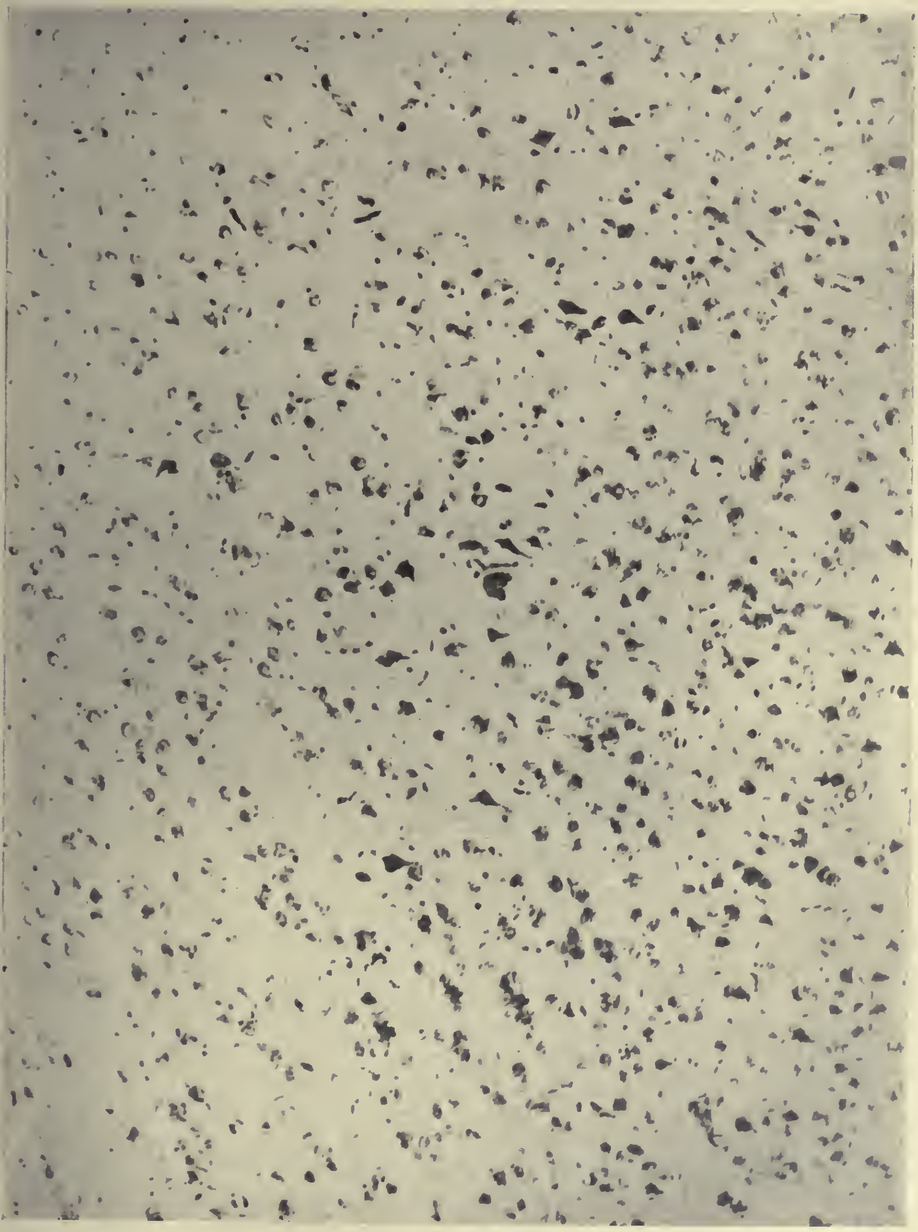

FIG. 8.—Cat: normal. Part of the cortex of the gyrus ectolateralis. Toluidin blue.

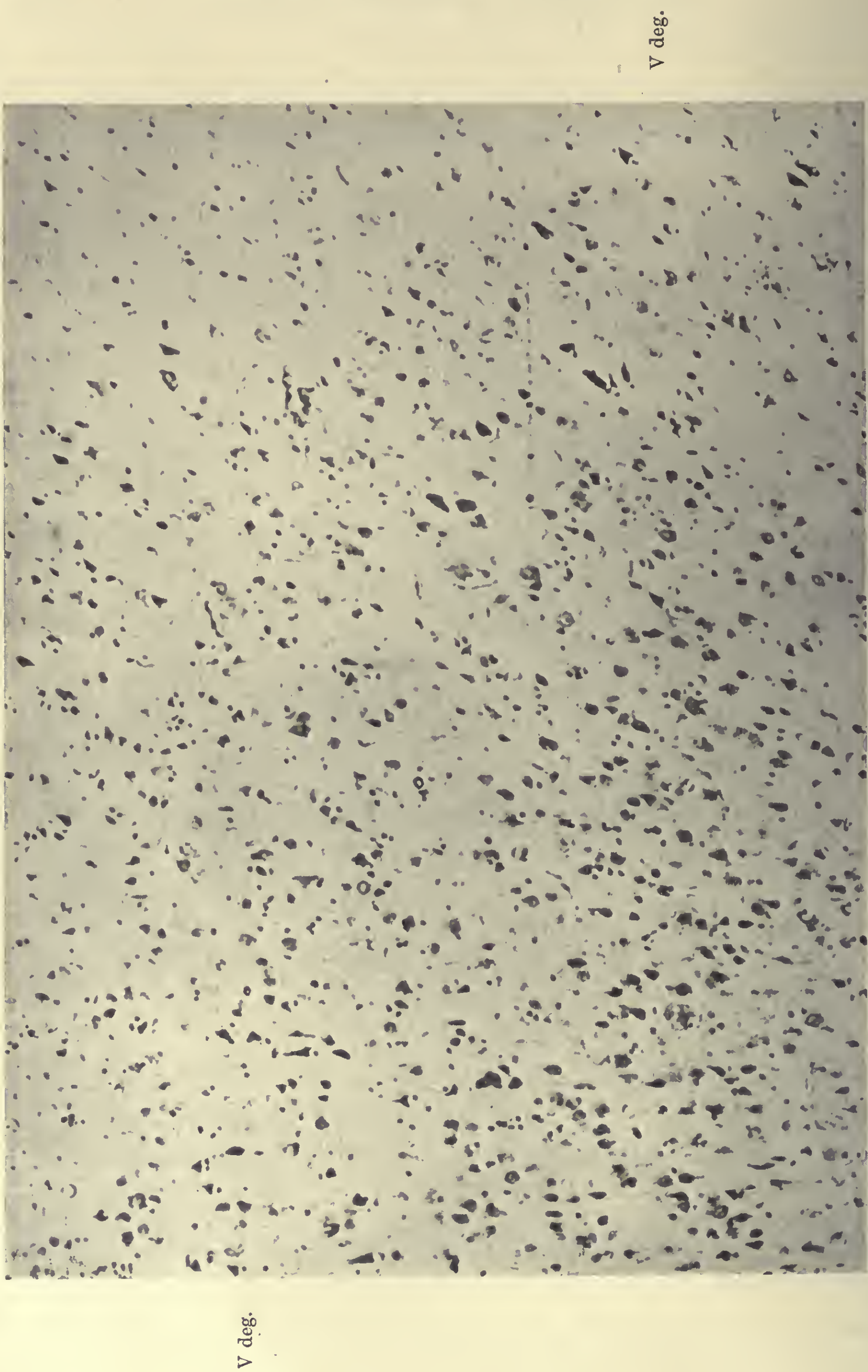

FIG. 9.—Cat: divisions of the posterior half of the corpus callosum. Part of the gyrus ectolateralis (corresponding with that in fig. 8).

discovered by the Weigert-Pal method. A pronounced loss of cells is very difficult to determine, but with strong magnification one finds, however, affected cells in the subgranular pyramidal layer, and possibly some in the sixth or polymorphic layer. The histological changes in these smaller elements are, however, exceedingly difficult to determine with positive certainty in material imbedded in paraffin, but as in the rabbit, there are no perceptible cell degenerations in upper cortical layers. Figs. 8 and 9, from the gyrus ectolateralis, illustrate these cell changes after sagittal section of the posterior half of the corpus callosum.

Pathological Cases.

In the introduction I alluded to the question whether cortical lesions cause secondary degeneration in the corpus callosum or not. That they do is admitted by most authors, as far as I am aware, except Kattwinkel. He examined, in Pierre Marie's laboratory in Paris, a great number of brains with very extensive cortical lesions and was never able to detect the slightest change in the corpus callosum. If the interpretation of this fact is difficult, the correctness of the observation can scarcely be doubted. It appears, however, to me that the large proportion of the fibres which have remained healthy is sufficient to account for the disappearance of all secondary callosal defect. On the other hand, Kattwinkel in his criticism of Dejerine's cases, is presumably right; the degeneration of the corpus callosum in these cases was not secondary, but primary. As a matter of fact, primary cortical softening cysts frequently occur accompanied by callosal lesions as Kattwinkel observed. One of my cases (No. 2) is a striking example of this.

A certain length of time is required for the total disappearance of secondary degenerated fibres of the corpus callosum. But it is evident that the duration of time between the onset of the lesion and death may be such that the degeneration of commissural fibres from the lesion may be clearly followed. Indeed, two of the following cases afforded this opportunity, as there were primary lesions of the corpus callosum and of the cortex.

Another method of determining the connexions of commissural fibres with certain cortical regions is possible when other fibre-systems in the immediate proximity are secondarily degenerated. In one case (No. 1) I was able to follow callosal radiations with certainty and to trace them later in preparations where all the fibre-systems were normal.

A.—Occipital Callosal Fibres.

Case 1 [52].—Hæmorrhage in the retrolenticular segment of the internal capsule, in the corpus geniculatum externum, and the frontal half of the sagittal strata of the occipital lobe. Secondary degeneration of the fasciculus longitudinalis inferior to its ending in the area striata in the occipital lobe.

Sections in the plane of the sulcus parieto-occipitalis were stained chiefly by the Pal method, with strong differentiation. The fibres of the corpus callosum from which the forceps and tapetum originate can be followed with absolute certainty from the forceps corporis callosi up to the occipital pole. It can be distinctly seen that fibre bundles separate gradually, both ventrally and dorsally, but the direction of the section makes it impossible to follow them into the different parts of the cortex at one level. But on the medio-ventral surface from the frontal end of the area striata to the occipital pole, fibres can be more or less clearly seen coming from the dorso-median or ventro-

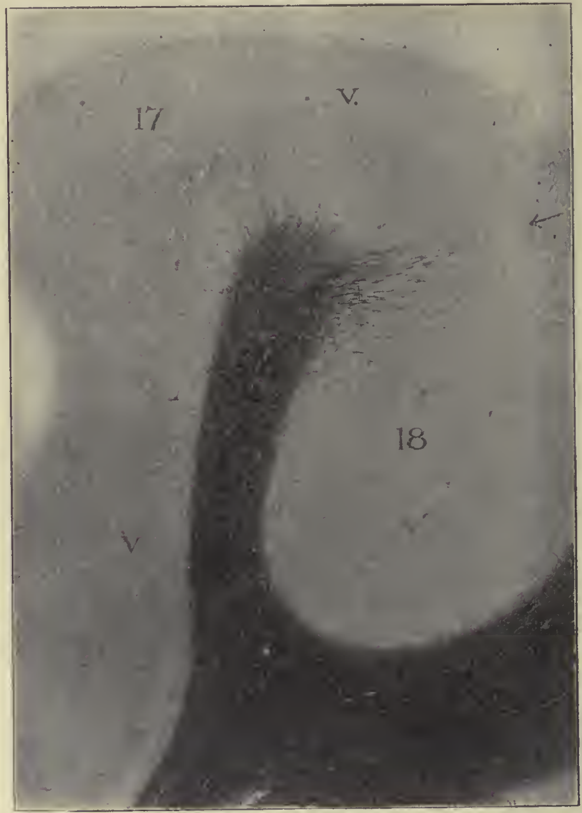

FIG. 10.—Case 1. ↓ Callosum fibres to field 18 (Brodmann) close to the Stria Vicq d'Azyr (V). Underlip of the sulcus calcarinus.

median boundary of the tapetum or the forceps and passing to the upper and lower lips of the sulcus calcarinus. They terminate on the immediate boundary of the cortical field adjoining the area striata (field 18 of Brodmann; visuopsychical area of Campbell, Mott, Bolton, and others). It may be stated with absolute certainty that not a single callosal fibre is connected with the calcarine cortex in the stricter sense of the term (area striata of Elliott Smith, field 17 of Brodmann). Fig. 10 shows the underlip of the sulcus calcarinus with the subcortical fibres of the lobus lingualis. These fibres are to a great extent degenerated, hence their pallor. One sees, however, a group of darkly stained fibres bending ventralwards from the white matter; these, which pass into the ventral cortex, can be followed continuously from the tapetum, 1·75 cm. from the occipital pole. This may also be seen in fig. 11. Both dorsally and ventrally in the regio calcarina these callosal fibres can be seen in connexion with the tapetum. The latter lies in the retrolenticular space, which is pale owing to total degeneration of the geniculo-cortical radiation. Owing to strong differentiation the Stria of Vicq d'Azyr is only faintly visible, but it is still distinguishable and of normal size.

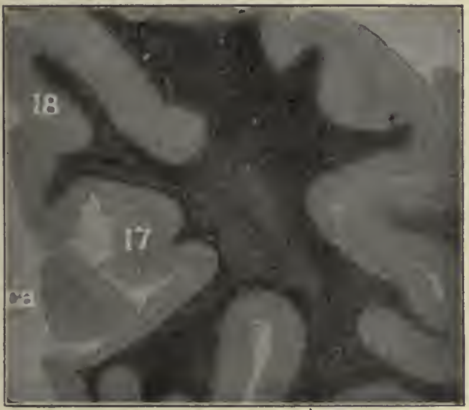

FIG. 11.—Case 1. Continuous bundle from forceps corpus callosi (tapetum) to field 18. ca = sulcus calcarinus.

Case 2.—Bilateral symmetrical softening of the cortex of the gyrus supramarginalis, gyrus angularis, a part of the lateral occipital convolutions extending down to the sagittal strata, and in the left hemisphere a softening in the calcarine region. The splenium is also softened, and there is secondary hæmorrhage in the posterior part of the corpus callosum.

During life there was serious disorder of speech (sensory aphasia), and visual disturbances, with partial mind-blindness.[1] The lesion in the right hemisphere had caused no demonstrable left-sided hemianopsia, but microscopical investigation showed that in all probability a small scotoma had been overlooked, as there was a localized secondary loss of cells in the corpus geniculatum externum.

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[1] The clinical and macroscopical observations are described in v. Valkenburg, "Zur Kenntnis der gestörten Tiefenwahrnehmung," *Zeitschrift für Nervenheilkunde*, 1908, Bd. xxxiv, S. 322, and Kurze Erwiderung, &c., *Zeitschrift für Nervenheilkunde*, 1909, Bd. xxxv, S. 472.

The softening in the corpus callosum was at first overlooked, and regarded as a secondary degeneration due to the approximately symmetrical cortical lesions; but closer scrutiny showed the primary nature of the lesion.

In addition to the splenium, the forceps and the tapetum of the right hemisphere were in part primarily, in part secondarily affected. In any case all the cortico-petal callosal fibres to the occipital lobe of the right hemisphere must have been destroyed, either primarily or secondarily. Consequently the callosal radiations to the cortex around the area striata could not be traced. Fig. 12, taken at about 2 cm. from the occipital pole, represents the underlip of the sulcus calcarinus. Where the callosal radiations adjoining the Stria of Vicq d'Azyr are normally found, they cannot be identified.

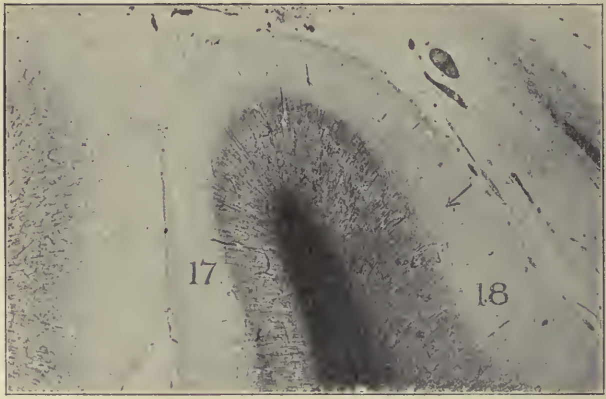

FIG. 12.—Case 2. Part of the regio calcarina (17); callosal radiation in field 18 absent, consequent on softening of the posterior part of the corpus callosum.

These fibres can be, however, more or less distinctly seen in the cortex in certain sections, especially in field 18 and near the area striata, in either the upper or lower lip of the sulcus calcarinus. It is obvious that they are shorter; while those of Case 1 could be traced above the Stria of Vicq d'Azyr, those of Case 2 remained distinctly beneath it. It was only in the posterior occipital part of field 18 that fibres which correspond as regards their vertical distribution in the cortex, with those of Case 1 are found. These are especially seen near the upper lip of the sulcus calcarinus.

Case 3.—Anophthalmos congenitus. Slight reduction of the sagittal strata in the occipital lobe, moderate dilatation of the posterior horn of the ventricle, and the occipital lobe, particularly calcarine region, diminished in size. The cortex of field 17 normal; Stria of Vicq d'Azyr of normal size in proportion to the other cortical layers.

This case [55] has been selected because owing to the shortening of the Stria of Vicq d'Azyr the contrast between the relations of the callosal radiations to field 17 and field 18 can be admirably reproduced in one photograph.

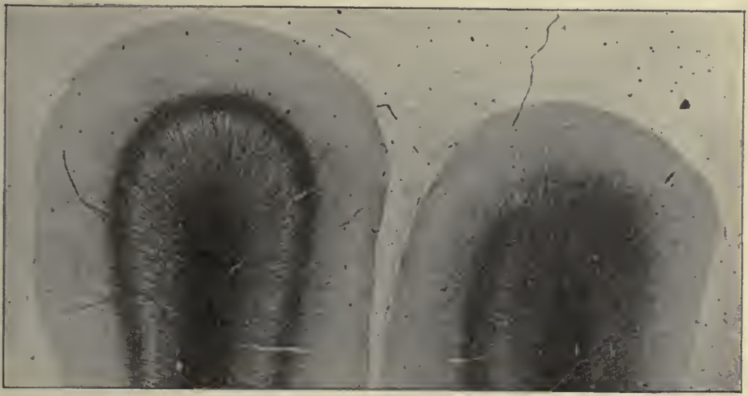

Fig. 13.—Anophthalmos. Lower and upper lips of the sulcus calcarinus; the first, in the area striata, without, the latter with callosal fibres.

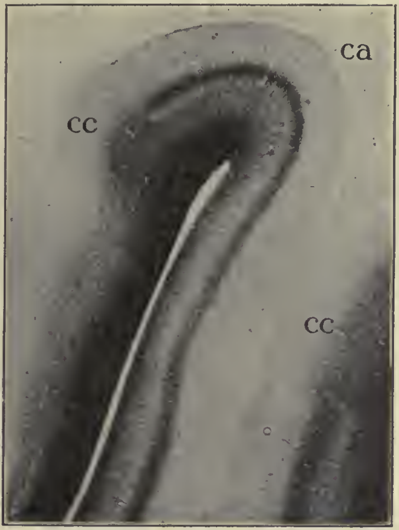

Fig. 14.—Case 3. Anophthalmos; regio calcarina. ca = sulcus calcarinus. cc = callosal radiations in field 18.

On fig. 13, taken almost 2 cm. from the occipital pole, both the calcarine lips are seen. The stria does not reach the depth of the sulcus calcarinus, which therefore belongs to field 18. On the other hand, the apex of the convolution which adjoins the under lip (lobus lingualis) belongs to field 17. We see long darkly stained fibres radiating from the white matter of the first convolution into the cortex, right up to the line of Vicq d'Azyr. The difference in calibre, as compared with the cortical radiation of the area striata, is very distinct. The surface of the under lip receives no callosal fibres; that this is not a peculiarity of the underlip, is proved by fig. 14. 2·5 cm. from the occipital pole a large callosal radiation may be seen in the wall of this convolution.

These fibres vary distinctly in length, the shorter ones only were found in Case 2. In this case of anophthalmos there exists a cuneo-lingual annectant gyrus by which the Stria of Vicq d'Azyr is interrupted in the sulcus calcarinus. In the walls of this deep convolution, which evidently belongs to field 18, the local callosal radiations can be easily found, as is shown by fig. 15.

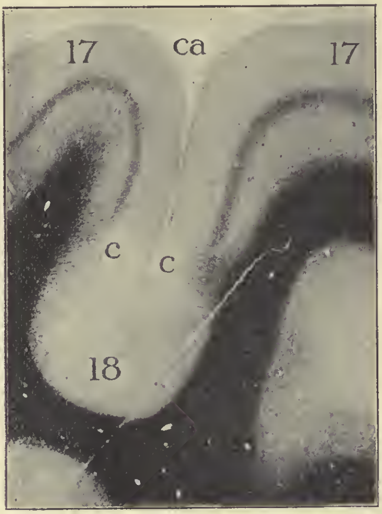

FIG. 15.—Case 3. Anophthalmos; Stria Vicq d'Azyr interrupted by annectant gyrus. ca = sulcus calcarinus. c = callosal fibres in field 18.

Normal brain.—It remains to consider the question whether the callosal cortical radiations can be recognized in normal brains. If the pathological cases had not paved the way, it would have been absolutely impossible to trace the callosal fibres into the cortex with any degree of certainty, as it is quite impossible to establish, in a normal preparation, a continuity between the forceps and tapetum, and the cortical radiations. The fibre radiations found in the margins of field 17, close to the ends of the Stria of Vicq d'Azyr, must be partly callosal. Fig. 16, representing a part of a section taken at

1·2 cm. from the occipital pole, shows these fibres near the dorsal boundary of the area striata. They are equally present at its ventral margin, and may be seen in the whole of this region of the cortex with variable distinctness.

The callosal fibres of the occipital lobe do not all stand in connexion with this small field, which surrounds the area striata. In Case 1, it was distinctly seen that both ventral (lobus fusiformis) and dorsal and dorso-lateral (gyri occipitales) fibres stretch from the tapetum to the cortex.[1] It was, however, impossible to follow them there in continuity, and it is therefore doubtful whether in these parts of the cortex the fibres of thick calibre also come from the corpus callosum. We must confine ourselves to exact observations, and these lead us to conclude that no callosal fibres originate or end in the area striata, but that they are connected with the cortex immediately around it. There is every probability that the long fibres which can be followed to the plane of the Stria of Vicq d'Azyr are cortico-petal; this seems probable from our observations in Case 2, as here the splenium and forceps were degenerated, and consequently all fibres originating from

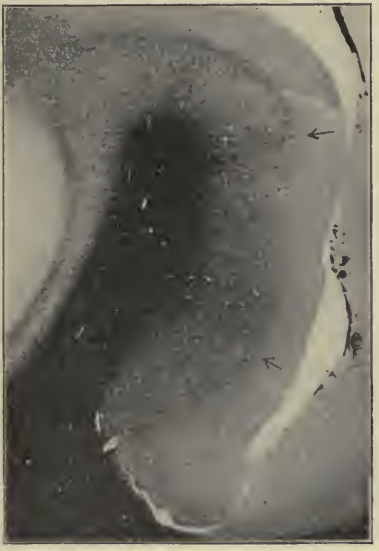

Fig. 16.—Normal brain. Upper lip of the sulcus calcarinus.
Callosal fibresin field 18 between ↓ ↓.

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[1] I will not enter on the question of the composition of the tapetum; it is certain in any case that it is partially composed of callosal fibres.

the left and destined for the right hemisphere, which pass through the corpus callosum, must have undergone secondary degeneration. As shorter fibres persist where the long cortex rays have disappeared, it is evident that those should be considered as cortico-fugal projection and callosal fibres. As the softening in the corpus callosum was fairly recent (there were masses of "Körnchenzellen" and hæmatocytes present) it is possible that these had not yet undergone retrograde atrophy. The existence of a few long fibres in the same place, especially in the extreme occipital region, is another difficulty. If we deny the possibility that a few callosal fibres escaped, which is certainly not probable from our sections, we might suppose that we have here to do with collaterals of cortico-fugal callosal fibres which originated in other parts of the homolateral occipital lobe. This, however, is not proved. This supposition would afford an explanation of the existence of Sachs' and Vialet's association system, which I have already assumed in a former paper [52] to consist of callosal fibres.

Whether the commissural fibres, which have their origin and termination in the cortex close to the area striata, are connected with homotopical parts of the opposite hemisphere, cannot be decided from my cases with absolute certainty.

The fact that the regio calcarina, in the narrower sense of the word, is not connected commissurally with the opposite side, is both physiologically and clinically of the highest importance. Beevor's observations on the marmoset are now confirmed in the human brain for the first time. Dejerine's anatomical conclusions are consequently erroneous, and the physiologico-clinical considerations which are based on a direct connexion of the two visual spheres, are groundless. Beevor looks upon the persistency of the hemianopsia, produced by a cortical lesion, as due to the absence of a commissural connexion, so that one hemisphere cannot compensate loss of the other. It is evident that this argument is not valid; a lesion which destroys the visual cortex in the one hemisphere, would inevitably destroy all the cells from which callosal fibres could arise, so that a cortico-fugal commissural connexion would be impossible. This pathological fact cannot be quoted in proof of the absence of a callosal connexion between the areæ striatæ; on the contrary, all arguments which rest upon the presence of such a connexion must be discarded. The greater part of the arguments relate to the explanation of the different forms of mind-blindness, but attention may be directed to Wilbrand's interpretation, accepted recently by Lenz [25], of the fact that, in hemianopsia of cortical origin, central vision generally remains intact. These writers assume that, frontally from the lesion, a connexion exists through the corpus callosum between the central visual tract in the affected hemisphere, and the calcarine region of the normal side. As they, together with Henschen, Flechsig, and many others, consider that the visual sphere is coincident with the area striata, such callosal fibres should consequently end in this area. The observations described above consequently disprove this hypothesis. We must henceforth consider the two primary end-stations of visual impulses in the cerebral cortex as, in a certain measure, independent of each other. It seems to me that, from a physiological point of view, this does not present any difficulty.

I fail to see any ground for assuming a connexion by which all impulses from one half of the visual field, after their arrival in the cortex, must be immediately placed in connexion with the centre for the other half of the visual field.

On the other hand, a commissural connexion is far more probable between the cortical centres from which eye movements can be evoked. Of late years Henschen [15] and others have assumed that the representation of the retina on the area striata should be so interpreted that in the upper lip of the sulcus calcarinus the two inferior quadrants of the visual field are represented, in the under lip the superior quadrants. According to Inouye's [17] theory, which appears to me extremely probable, there exists, moreover, a localization of the more central parts of the visual field (retina: fovea centralis) in more caudally situated regions of the area striata. The peripheral parts of the retina are, moreover, represented at the periphery of the area striata. It is stimuli from these peripheral portions of the retina that cause most eye movements of visual origin. It is true that the movements of both eyes are bilaterally co-ordinated from one hemisphere, and the probability is, therefore, greater that normally both hemispheres co-operate in their execution. On these physiological grounds it seems very probable that the callosal fibres connect homotopical areas, but this by no means excludes a heterotopical connexion. The experimental stimulation of the monkey's brain by Sherrington [45], who found foci for conjugated eye movements exactly along the sulcus calcarinus, supports this view. It appears to me indeed probable that Sherrington and Grünbaum stimulated chiefly this region. This is the more likely because Minkowski [32] also found that faradization of the area striata itself in dogs produced no effect, though he could excite eye movements from the second

"Urwindung" in its immediate proximity. The closely adjoining radiation of callosal fibres into the part of field 18 in the cat's and human brain, which is adjacent to the area striata, shows that the here incoming and outgoing commissural impulses must be strictly localized, as they are excited by relatively very circumscribed peripheral retinal impulses and are concerned in the production of accurate and precise movements of the eye-balls.

The dispute in regard to the localization of the fovea centralis in the cortex of the lobus occipitalis is still unsettled. From different clinical and pathologico-anatomical observations of late years, which cannot be discussed here, it seems to me that it is most probably represented in the posterior part of the area striata. In most cases this area extends round the occipital pole, to the lateral surface of the hemisphere.

If so, only a relatively small part of the extreme occipital region of this area is bounded by callosal radiations. The so-called "cortical macula" should lie further away from the commissural fibres. If this hypothesis, for which support may be found in the work of Niessl v. Mayendorf [38], Inouye [17], and others, should prove to be true, it would agree with these physiological considerations based on the distribution of the callosal radiation, as the only part of the retina from which reflex conjugate movements cannot be excited is the fovea centralis. That in mice and rabbits, which have no fovea centralis, the occipital lobe receives no callosal commissure-fibres, is no argument against my views. In these animals, which have a very small, if any, binocular visual field, the ocular movements are chiefly of vestibular origin, and do not result from visual impressions; the latter cause rather head- and neck-movements.

The following is another general argument to account for the total lack of a commissural connexion between the two areæ striatæ. It is in my opinion a general law in the structure of the central nervous system, that the anatomical structures concerned with different functions at different levels in their projection-course are similarly arranged. Undoubtedly there exists an extensive commissural connexion between the primary motor centres of the brain-stem, for instance, the oculomotor nuclei, but such has never been shown to exist between the primary optic centres of the mesencephalon and thalamencephalon. The posterior commissure, whose position between and frontal to the corpora quadrigemina anteriora or the lobi optici of the amammalia, might suggest that it is a commissure between them, has not been shown to have this function. Sections of the posterior commissure in rabbits and cats never produce cell degeneration in the optic part of the anterior corpora quadrigemina, nor in the corpus geniculatum externum. The same is true for the lamina commissuralis tecti. As the sensory and motor representations of the eye-ball in the cerebral cortex are, in all probability, built on the same plan, though naturally modified in conformity with the more complicated functions of the fore-brain, it might be assumed that there exists a commissure between motor ocular centres, as indeed has been demonstrated in the monkey, and possibly a few other mammals. Sherrington [46] made its existence probable by obtaining conjugate ocular movements by stimulation of the splenium in monkeys. On the other hand, no connexion between the primary visual cortical centres through the corpus callosum would be expected. As I have shown, it is absent.

B.—Callosal Fibres of the Regio Rolandica.

Case 4.—Softening of the corpus callosum in the right hemisphere from the gyrus cinguli to the truncus corporis callosi. It commences caudally in the transverse plane that passes through the posterior part of the corpus geniculatum externum and extends frontally to the motor zone. In the left hemisphere a softening was present in the base of the gyrus supramarginalis, and some small scattered cysts in the cortex. Two sclerotic patches were found in the fasciculous longitudinalis inferior of the right hemisphere.

This case was an old woman suffering from arterio-sclerosis; nothing particular is known of her clinical symptoms. There is no history of apraxic disturbances, but presumably the patient's mental state made an examination on this point impossible.

The part of the callosum which lies in the frontal plane of the Rolandic region was destroyed by the softening, partly in the right hemisphere dorsal to the lateral ventricle, and partly in the median line; all commissural fibres in this part have been interrupted.

Fig. 17 shows the greatest extent of the softening. It represents a part of a section which contains the dorsal third of the gyrus centralis anterior. At this level only, the cyst extends to the central part of the lobulus paracentralis; elsewhere it remains below the sulcus calloso-marginalis. The corona radiata is practically unaffected, and in this level the left hemisphere was intact. A pale strip can be traced from the cortex of the gyrus centralis anterior towards the cyst; as it diminishes in width, and as the number of degenerated fibres it contains evidently decrease in number as it approaches the corpus callosum, it must have contained fibres which were not connected with this. It can be followed only to the motor cortex; its radiation into the cortex is better seen in fig. 18, which lies 1 cm. frontal to the occipital end of the callosal cyst. The degeneration extends into the cortex and there spreads out fan-wise. The tangential fibres are as numerous as in the adjoining cortical regions, but the latter contain the ordinary radiary fibres, which are entirely absent in the affected area. The pale strip in the centrum ovale gradually becomes narrower towards the softening in the corpus callosum; a part of its fibres must undoubtedly have originated from this. Though no primary lesion exists in the cortex in this section, as is shown by the persistence of the horizontal fibres, there is a small vascular necrosis slightly frontal to it to which a part of the degeneration of the radiary fibres may be due. We may consequently consider the fan-shaped fibre loss as the result of both a cortico-fugal and cortico-petal degeneration; the first involved projection and commissural fibres, the second only the latter. The projection fibres belong

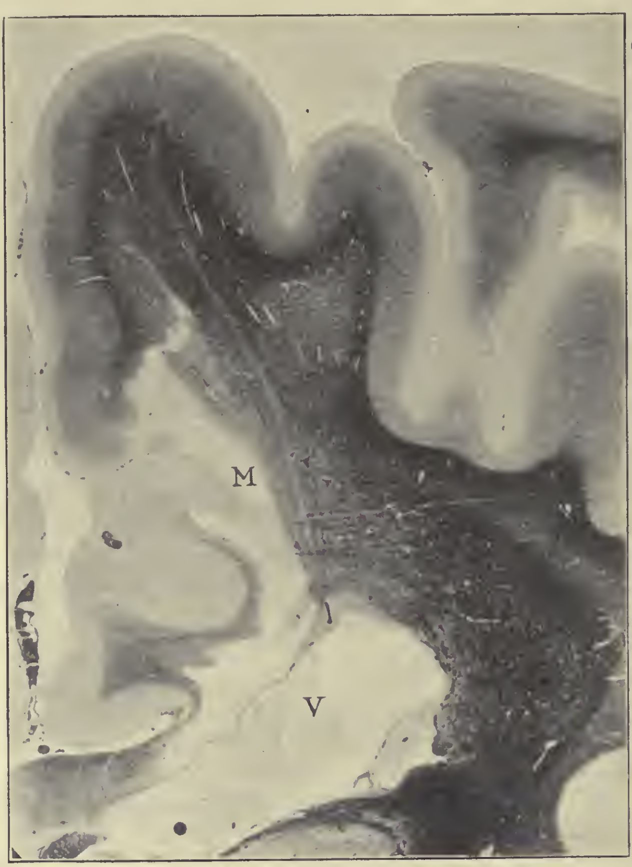

FIG. 17.—Case 4. M = softening. V = lateral ventricle. Degeneration strip from M to the cortex of the precentral gyrus.

to the tractus cortico-spinalis, which we know originate in the fifth layer (lamina ganglionaris, Brodmann); all long cortical rays which have disappeared are therefore callosal fibres. I draw attention to the localized manner in which commissural bundles radiate into this cortical "motor" region.

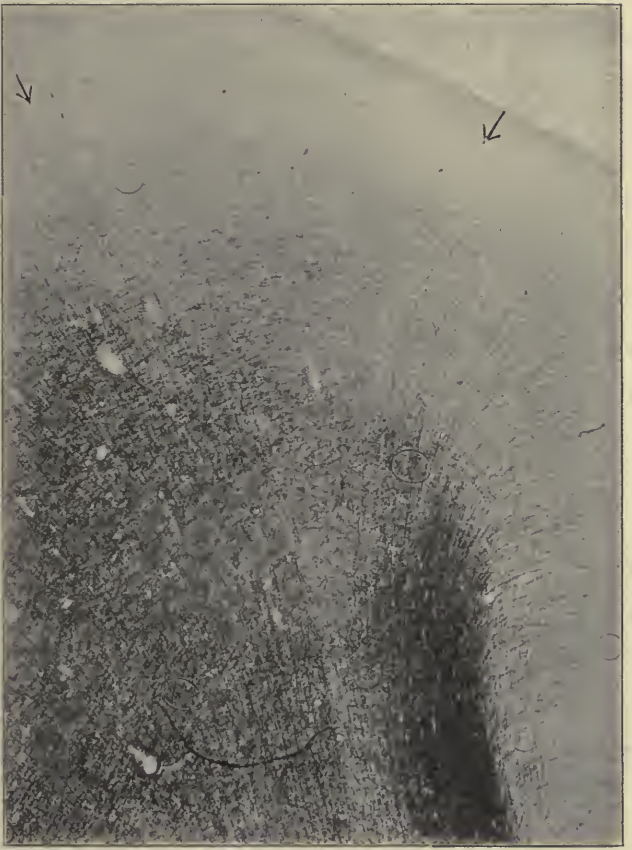

FIG. 18.—Case 4. Precentral gyrus, upper part. Fan-shaped degeneration of radiary fibres between ↓ ↓.

In a section 2·2 mm. in front of fig. 18 the effect of the vascular lesion has disappeared; the degeneration strip in the centrum ovale and the white matter of this convolution is scarcely visible, though the callosal softening is unaltered. Only the longer cortical rays that reach the superradiary network have disappeared. From this we may conclude that the longer fibres radiating into cortex are cortico-petal callosal fibres. It is of course possible that commissural fibres also end more diffusely in these convolutions, as is shown in fig. 19. This represents the gyrus centralis anterior of the opposite side

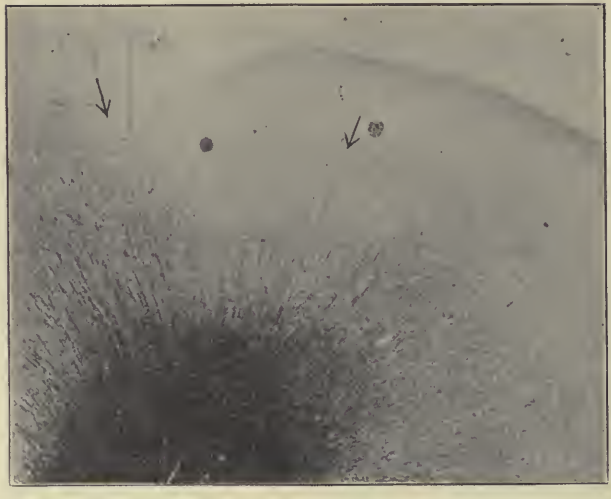

FIG. 19.—Case 4. Precentral gyrus, middle part, left. The long intracortical callosal fibres (cortico-petal) are degenerated between ↓ ↓.

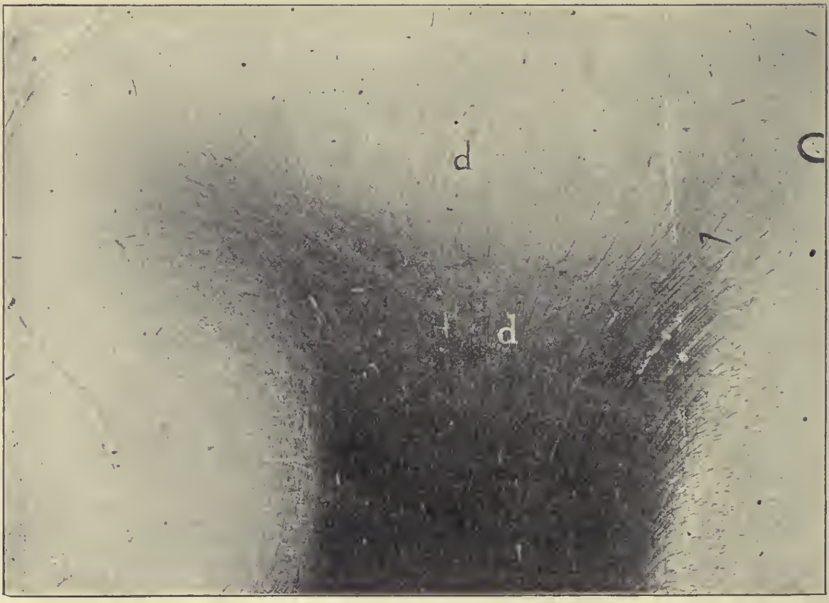

FIG. 20.—Case 4. Postcentral gyrus, right, 5 mm. behind the cyst. d d = secondary degenerations of infracortical and cortical callosal fibres.

1·5 mm. farther forward; the callosal lesion lies on the right. In the vertex of the convolution in which there is no sign of any primary lesion, it is clearly seen that many long radiary fibres have disappeared. It is true that the limits of the degeneration can be still defined, but it is evident that the loss gradually diminishes from its middle towards both sides.

A distinctly more diffuse character of fibre loss is seen on the other hand in the gyrus centralis posterior, which shows a diminution of the radiary fibres, but nowhere a localized degeneration.

A corresponding but far more striking loss of fibres is visible in the posterior central convolution of the right hemisphere, into which the callosal lesion extends. Fig. 20, a little more than ½ cm. caudal to the commencement of the softening, shows no secondary degeneration in the fibres of the gyrus centralis posterior, except immediately below the cortex. It is evident that the secondarily degenerated fibres coming from the lesion, unite before radiating inwards. The entire dome of the convolution is marked by a paucity of radiary fibres, though they are nowhere entirely absent; towards the sulci, especially on the dorsal side (to the left on the figure), the increase of the radiation is very gradual.

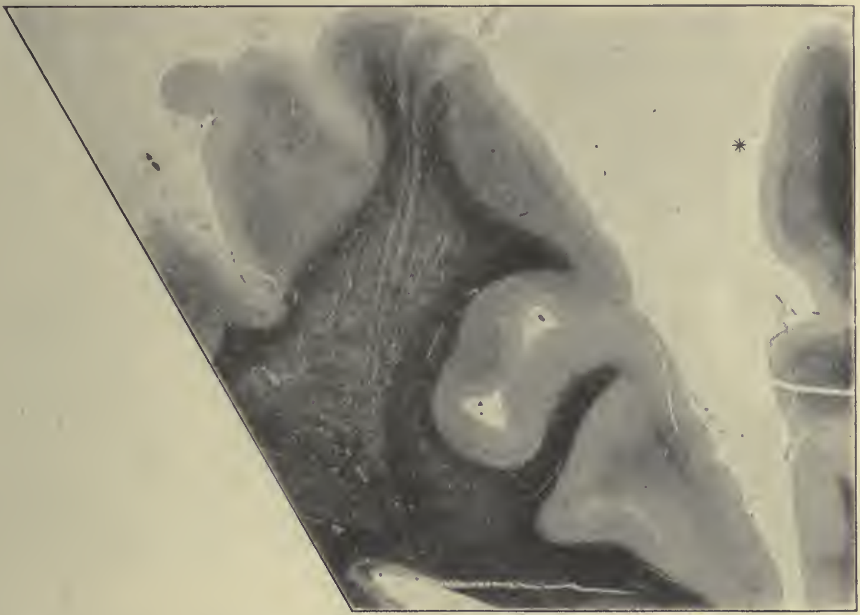

FIG. 21.—Case 5. Cortico-fugal degeneration, partly of callosal fibres from the upper part of the left precentral gyrus; * indicates a spot in the right precentral gyrus where secondarily callosal fibres are lost.

Case 5—A large softening in the left hemisphere, extending from the occipital pole to the gyrus centralis posterior on the lateral convexity, and involving the dorso-lateral part of the sagittal strata. Scattered cortical vascular lesions, especially in the gyrus centralis anterior.

A softening in the anterior part of the gyrus fusiformis and lobus lingualis of the right hemisphere which also involves the ventral (horizontal) part of the sagittal strata.

There is very little known of the history of this patient; she was "demented" and too confused to be examined. The part of the brain which is of special interest is the Rolandic region, and the cortical lesions is in the left gyrus centralis anterior (fig. 21). In the anterior central convolution two small softenings are seen, from which two narrow strips can be followed to the dorso-lateral angle of the ventricle; during their course they become gradually smaller, especially as they pass through the corona radiata. Part of the degeneration can be followed into the supraventricular part of the corpus callosum, in which it speedily disappears. We have here a combined corticofugal fibre-degeneration of the projection and commissural systems. The other strips of degeneration, running more or less parallel, come from more frontally situated cortical lesions and follow a similar course. When we endeavour to follow these secondary degenerations into the right hemisphere, it is seen that, as in the corpus callosum, they cannot be identified in the centrum ovale; they can be recognized only at the termination of some of the subcortical fibre cones, and especially in the cortex. This absence of visible

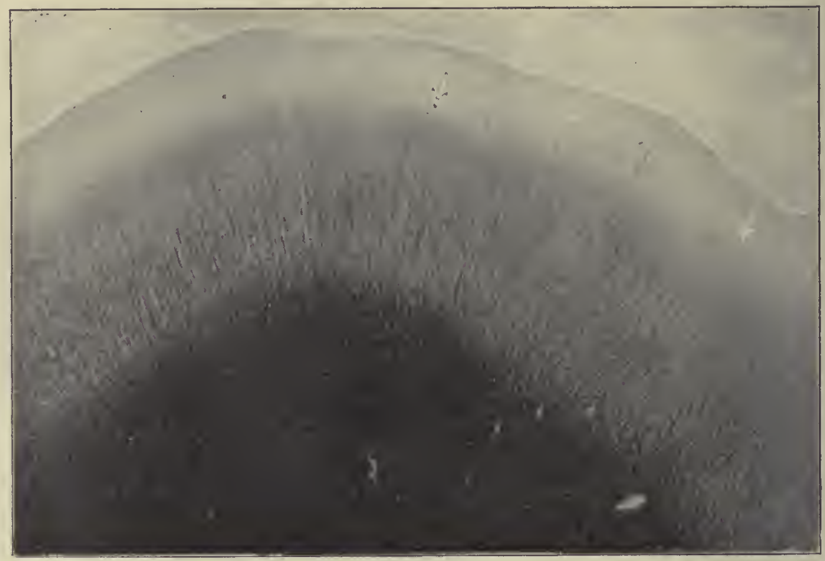

FIG. 22.—Case 5. Upper part of the right precentral gyrus. 1¼ cm. frontal to fig. 21. Loss of long cortico-petal callosal fibres between ↓ ↓.

continuity renders it impossible to state with certainty from which primary cortical lesions of the left hemisphere the lost radiary fibres in the right come. As the degenerated fibres come exclusively from the left gyrus centralis anterior, it may be concluded that this convolution is wholly responsible for them; it was chiefly its dorsal part, the "leg centre," that contained these softenings. Even in the slightly magnified figure a distinct loss of radiary fibres [at *] can be seen in the right lobus paracentralis, though the tangential fibres persist. Fig. 22 is a more strongly magnified photograph of the anterior part of the right gyrus centralis anterior, close to the dorsal margin, 1¼ cm. in front of fig. 21. There are several confluent softenings in the cortex of the corresponding areas in the left hemisphere, from which pale strips can be followed that partly disappear in the corpus callosum. The loss of cortical rays visible in the figure is in the exactly homologous area of the right side of the brain. There is a marked reduction of the long cortical rays, but the short ones are not definitely diminished in number. The boundaries of the region where the loss is seen are tolerably sharp on each side. As the cortical lesions in the Rolandic region of the left hemisphere are limited to the gyrus centralis anterior, and to particularly the "leg centre," this case may throw some light on the ending of those callosal fibres in the gyrus centralis posterior on the right side. In sections 7½ mm. behind fig. 21, there is not a trace of any defect in the rays of the cortex of the dorsal part of the left gyrus centralis posterior. On the other hand, there is a distinct fibre loss in the homologous area of the right hemisphere, but it is not nearly as sharply defined as in the gyrus centralis anterior. The entire long cortical radiation has become much "thinner." The Baillarger layer is preserved as well as the tangential fibres. The limitation of the cortical lesions in the left hemisphere to the dorsal part of the gyrus centralis anterior is by no means absolute; it is, however, probable that those situated elsewhere have caused corresponding contra-lateral degenerations. In the transverse plane of the corpora mamillaria, about ½ cm. frontal to the section from which fig. 22 is taken, we find a cyst in and under the cortex of the middle of the anterior central convolution, which is separated from the cortical lesions in the dorsal part of this convolution by normal brain tissues; both the cortex and the white matter ventral to it are intact. In the sections of the right hemisphere from this region we find a slight rarefaction of subcortical fibres due to secondary degeneration from the lesion in the left side, but a few degenerated cortical rays only are found in the homologous region on the right side; the degeneration passes further distalwards and reaches the cortex after having passed the base of the sulcus centralis. Finally, the diffuse degeneration in the subcortical substance of the convolution penetrates the cortex of the gyrus centralis posterior in about the same horizontal plane as the middle of the gyrus centralis anterior. Its termination lies in a sagittal direction about 1½ cm. behind the origin of the degenerated commissural fibres. The cortical rays are diffusely diminished in number. Notwithstanding the numerous lesions in this half of the fore-brain, the fibre content of the posterior central convolution, if not normal, is at least much greater than on the right side. As mentioned above, the ventral and dorsal parts of the convolution adjoining the softening, which occupied the middle part of the gyrus centralis anterior (the "arm centre"), were unaffected. On the other hand, the extreme dorsal part of the anterior central convolution ("leg centre") contained small foci of softening. The secondary degenerations resulting from these lesions in the cortex of the gyri centrales anterior and posterior on the right have been already described; they are apparently confined to the extreme dorsal parts of these convolutions. In the regions immediately ventral thereto, as in the cortex ventral to the middle of the two gyri centrales, the fibre loss is far less distinct or is entirely absent. One seems justified in seeking the cause for this difference in the extent of the cortical and subcortical softenings in the left anterior central gyrus.

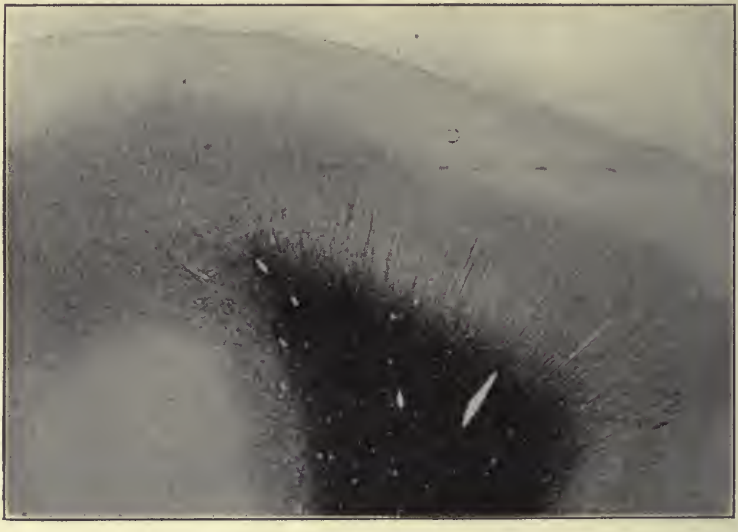

Fig. 23.—Case 5. Middle part of the right postcentral gyrus. Diffuse degeneration of callosal fibres.

Further caudalwards where the left occipito-parietal lesion falls in the section, the conditions become too complicated to determine with certainty the cause of the degeneration of the cortical rays on the right side. It is, however, remarkable that in a section through the splenium the cortical rays in the right operculum are diffusely degenerated.

C.—Frontal Callosal Fibres.

Case 6.—Left hemisphere: necrotic cysts filled with fluid which isolated the cortex of the entire temporal lobe, the greater part of gyrus centralis posterior, and almost the whole of the parietal lobe, but the fibræ propriæ were almost everywhere preserved. Subcortical softenings in the ventral and most dorsal parts of the gyrus centralis anterior, and in the base of F^1 and F^2. The white matter of F^3 (Broca's centre) was also involved. In the right hemisphere a single small softening in the temporal lobe (T. 3).

This case [53] was a woman of about 60 years of age, who had been ill for a number of years. Her symptoms were :—

Paresis of the right side of the face; helpless, hemiplegic gait, and Babinski's sign and foot-clonus on the right. Loss of kinæsthesia and astereognosis in the right hand; nowhere complete tactile anæsthesia; localization of touch in the right arm only slightly disturbed. No hemianopsia, but from investigation of the brain it is evident that there must have been a scotoma, as the left external geniculate body was partially degenerated.

Almost total aphasia, principally sensory, but she could still use a few words easily and properly; complete alexia and agraphia. She never used the right hand spontaneously; it was, however, not paralysed as even delicate movements of the fingers were possible.

Motor apraxia of the right arm, and of the tongue and face. The apraxic disturbances in the left arm were extremely slight; they were generally only evident when two-handed movements were attempted.

This case afforded very little fresh information on the localization of apraxia. Both the gyrus supramarginalis (Liepmann) and a part of the three frontal convolutions immediately in front of the motor zone (Hartmann) were softened subcortically; and the greater part of the white matter of the gyrus centralis posterior and the lobus parietalis were destroyed. The aphasia was due to the temporal lesions, which extended to F^3 along the insula.

The corpus callosum was nowhere directly affected, but it was much reduced, especially in its centro-parietal part; its vertical measurement was not more than 1 mm. No secondary degeneration could be detected in it; but the considerable shrinkage it had undergone was certainly a result of the enormous loss of substance in the left hemisphere. The destruction of this was so extensive that it is impossible to determine definitely a connexion between the affected callosal radiations in the right hemisphere and special regions of the left cortex.

I will rather, therefore, use this case to demonstrate a few bundles, which from their immediate proximity to the corpus callosum are of importance in the study of the latter.

Two fibre-systems must be considered :—

(1) The fasciculus subcallosus (Muratoff [36]), fasciculus nuclei caudati (Sachs [43]), or fasciculus longitudinalis medialis (Anton u. Zingerle [1]).

It is usually held that this system has nothing to do directly with the corpus callosum. Muratoff showed that certain of its fibres degenerate in consequence of lesions of the regio sigmoidea in dogs. Anton u. Zingerle demonstrated connexions with the capsula externa and stated that it has probably numerous connexions with the cortex of the fronto-parietal region and with the basal ganglia.

My case enabled me to confirm this latter view, as owing to the degeneration of a large part of the white matter of different convolutions, the remaining fibres could often be followed over a considerable extent in one section. Fig. 24 shows a part of a frontal section through both hemispheres; only the most ventral part of the left gyrus centralis anterior and the upper and the middle portions of the gyrus frontalis are situated in this plane. A great portion of the corona radiata is degenerated, but projection-fibres from the gyrus centralis anterior (facial and tongue centres) persist. These pass transversely through the dorsal part of the external capsule, and dorsally to the nucleus lentiformis to the lateral part of the internal capsule.

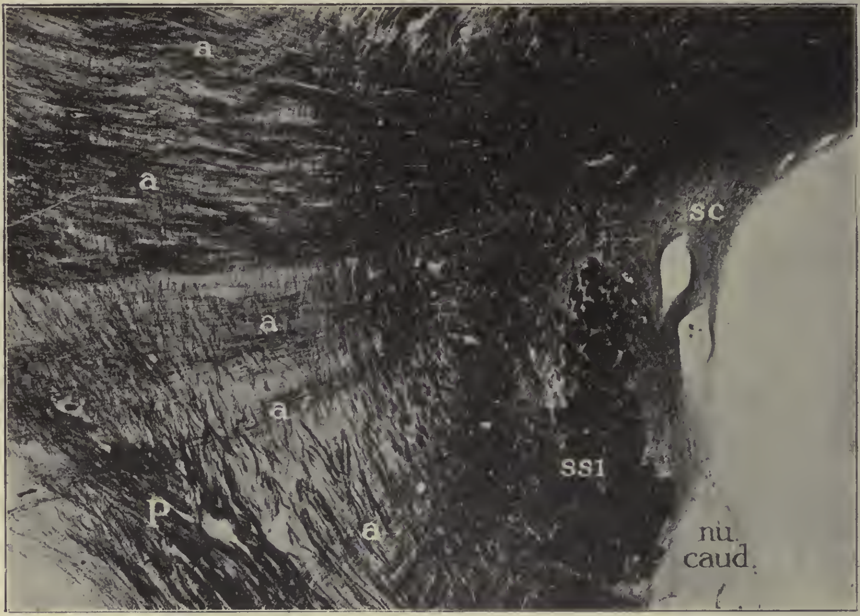

Fig. 24.—Case 6. a = fibres from cortex to fasciculus subcallosus (partly degenerated and to corpus callosum. sc = fasciculus subcallosus. ssi = stratum sagittale internum. P = pyramidal tract.

Separated from these by a broad pale zone the medial fibres of the corona radiata pass to medio-dorsal portions of the frontal gyri. Both bundles are traversed vertically by finer fibres, but the latter are partially degenerated, and only certain bundles are preserved. They can be followed from the external capsule and from the lower part of the gyrus centralis anterior to the fasciculus subcallosus, where they terminate abruptly. In the most dorsal part of the figure one sees better preserved fibres coming in exactly the same manner from F^2; these can be also partly followed to the fasciculus subcallosus, partly to the lateral region of the corpus callosum, and a similar connexion exists with F^1. In fig. 25, from a section 1·2 cm. in front of the former one, the fasciculus subcallosus is greatly increased in volume.

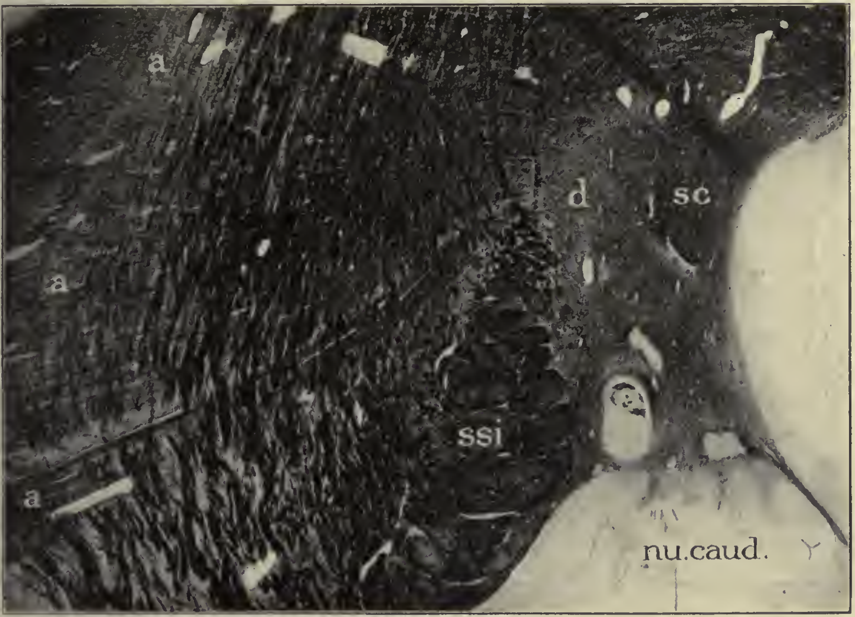

Fig. 25.—Case 6. a = fibres from cortex to fasciculus subcallosus (partly degenerated) and to corpus callosum. sc = fasciculus subcallosus. ssi = stratum sagittale internum. d = degenerated part of fasciculus subcallosus.

The lateral part of F^3 is partially degenerated in consequence of the subcortical cyst in F^3 and F^2, and a pale strip can be traced from it to the fasciculus subcallosus.

Similar connexions between all the fronto-parietal convolutions and the fasciculus subcallosus can be seen further posteriorly where this latter extends, behind the nucleus caudatus, into the "substance subependymaire" (Dejerine). The same connexions, less in number, exist between cortex and the fibre mass along the posterior horn (part of the tapetum).

The fasciculus subcallosus in these and more frontal sections is much larger than it appears. The coarser and more darkly stained fibres in the neighbourhood of the lateral ventricle surround it and largely hide it from view. The fibres of the corpus callosum lie dorsal to the ventricle, but are separated from it by the fibres of a peculiar bundle which we must now consider.

(2) Fasciculus occipito-frontalis; stratum sagittale internum (Anton u. Zingerle), or reticuliertes Stabkranzfeld (Sachs). This bundle appears lateral to the ventricle at the level of the retrolenticular part of the internal capsule, immediately lateral of the tail of the nucleus caudatus. It is undoubtedly in connexion with the internal capsule as Anton u. Zingerle, Sachs, and others rightly maintain. Frontally the bundle increases considerably owing to accession of fibres from the median part of the capsula interna, as figs. 24 and 25 clearly show. From the dorsal margin of the bundle fibres which pass off in a dorsal direction may be followed to the lateral part of the corpus callosum. Wernicke therefore came to the conclusion that these fibres pass from the capsula interna into the corpus callosum, and from the study of different preparations, both normal and pathological, I have more than once been inclined to accept this view. But the view of Anton u. Zingerle is certainly correct, as, especially in more frontally situated sections (fig. 25), the fibres can be traced from the tip of the bundle, through the callosal radiation, towards the dorso-median gyri. From the study of Case 4, in which this bundle was to some extent atrophied, I consider that it radiates into the gyrus frontalis superior and probably to the gyrus calloso-marginalis.

A case in which the corpus callosum, except for a very small part of the splenium, was destroyed during the first year of life, confirmed this supposition [52]. In addition to the corpus callosum, however, the entire mesial wall of the frontal lobe and the paracentral lobule were destroyed. As the stratum sagittale internum persisted, though considerably diminished, it must necessarily be also connected with the more dorsal portions of the frontal lobe. My preparations give the impression that this bundle forms the projection-radiation of the dorsal part of the lateral nucleus of the thalamus. The radiation terminates for the greater part in front of the lesion, which extended to the base of the upper and middle frontal convolutions; Case 6, in which the bundle was equally well preserved on both sides, shows this clearly. In summarizing our observation on the callosal radiations of the regio Rolandica, and the frontal lobe, I must first emphasize that this investigation has by no means solved all the questions. In my anatomical conclusions I will simply confine myself to the facts personally observed.

Callosal fibres can be far less distinctly followed into the cortex in the regio Rolandica than in some parts of the occipital lobe. In this region there is a well-defined isolated system (forceps-tapetum), and with a favourable plane of section and proper staining the fibres can be continuously followed into field 18, and possibly elsewhere. But the fibres of the body of the corpus callosum cannot be traced directly to the cortex in transverse sections; part of these turn ventralwards round the lateral ventricle, mesial to the corona radiata, but the greater part pass dorso-lateralwards and in an oblique sagittal direction. I can confirm the description of Anton u. Zingerle [1]. Moreover the ending in the cortex of the fibres that ascend vertically from the lateral part of the corpus callosum, is far more diffuse than in the occipital lobe.

The cortical lesions in Case 5, particularly those in the anterior central convolution, and the secondary fibre-degeneration resulting therefrom, prove that cortico-fugal callosal fibres run in compact bundles between the cortex and the lateral portion of the corpus callosum; they run almost vertically to it. Further, as Case 6 shows, there is a great danger of confusing the association fibres of the fasciculus subcallosus with true callosal elements; this error is the more possible, as the fasciculus subcallosus is covered by callosal fibres over a greater area than one would believe from normal preparations. In this respect the sections of Case 4 are important. Indeed, while the corpus callosum was completely destroyed in the Rolandic region of the right hemisphere, the fasciculus subcallosus was practically intact. Bundles which could be followed, however, from the cortex to the cyst were evidently destined for the corpus callosum. These degenerations were remarkably similar to those in Case 5; this was in consequence of the small cortical lesions which produced a corresponding fibre loss. There is, however, a distinct difference; in Case 4 the fibre loss extends further than the cortical disturbance, and, as fig. 18 so strikingly shows, the degenerated radiary fibres occupied a fan-shaped area towards the cortex. The conclusion one would easily draw from a study of the preparation from which fig. 18 is taken, is that the degenerated fan consists of degenerated cortico-petal callosal fibres, resulting from the callosal softening. The fact that a cortico-fugal callosal degeneration (Case 5) certainly produces exactly the same fibre loss in the centrum ovale must, however, act as a deterrent from drawing such a conclusion. Moreover, a further investigation of the series will prevent us from doing so, a cortical lesion being found in the immediate proximity. This justifies the conclusion that the same part of the gyrus centralis anterior, from which compact fibre bundles arise, also receives cortico-petal commissural elements.

When a lesion which does not involve the cortex produces an isolated commissural degeneration, the disappearance of the cortico-petal callosal fibres alone is not sufficient to cause a well-defined tract of degeneration up to the cortex. It necessarily follows that the callosal radiation must be more or less diffuse. Case 4 (fig. 18) proves, however, that in the gyrus centralis anterior this diffuse character is not absolute, as callosal fibres from the one hemisphere end where other callosal fibres arise. The latter, however, are fewer in number; it is evident that the cortico-fugal degeneration nowhere consists exclusively of commissural fibres. It thus follows that besides a homotopical connexion, which must certainly be admitted, there is also a heterotopical one. I cannot make out in what relation the termination of these fibres stand to the place of origin of the callosal fibres. It was only in the gyrus centralis anterior that I could with certainty determine the close correspondence in their origin and termination. The illustrations of cortex of the undamaged hemisphere in Cases 4 and 5 show this also. Moreover, the preservation of the short cortico-fugal cortical radiations, and the disappearance of the longer cortico-petal rays, are here visible. It is evident that the cortical fibre degeneration due to the callosal lesions is equally diffuse in the gyrus centralis posterior, while the local loss of fibres is less circumscribed than in the gyrus centralis anterior. I cannot determine with certainty the origin of callosal fibres in the gyrus centralis posterior. In the cases with cortical lesions, such as those described in gyrus centralis anterior, I never saw such distinct fascicular degenerations.

I believe I may be justified in stating that in the *posterior central convolution* :—

(1) The relation of the origin and termination of the callosal fibres is not definitely local.

(2) The ending of these fibres is relatively diffuse.

(3) Fibres end here which come from the contra-lateral gyrus centralis anterior, and to some extent at least the origin and termination both in front and behind the sulcus centralis are situated in the same horizontal level.

On the other hand, the *anterior central convolutions* are :—

(1) Connected *homotopically*, in the sense that the origin of cortico-fugal fibres is more or less surrounded by a radiation of fibres from the homologous spot on the opposite side; it is doubtful if there

exists a heterotopical connexion between the gyri centrales anteriores; I have no argument in favour of it.

(2) They are connected with the contra-lateral gyrus centralis posterior in the manner described above. The fibres which form this heterotopical connexion are apparently far more numerous.

It is possible that the relations of the callosal rays in the prefrontal gyri can be better followed than those of the centro-parietal region, owing to the more sagittal course of the commissural fibres around the cornu anterius, resembling in this respect the forceps and tapetum in the occipital lobe. I have, however, not been able to collect such positive information with regard to the frontal lobe as Case 1 afforded of the relations of the commissural fibres to Brodmann's field 18. It was only the region of the base of the third frontal convolution in Case 6 which could bring light to bear on this. In the first place it results from these preparations, that, even when there is not a primary callosal lesion, the great commissure decreases very considerably in volume owing to the destruction of a part of the centrum ovale and of the centro-parietal region, as indeed might be expected. It is very difficult to follow in continuity fibres from the frontal and temporal convolutions in the corpus callosum, but it is certain that they have a very similar course to those that definitely run medialwards into the complex of the fasciculus subcallosus. In Case 6 it is not possible to determine whether in certain places these radiary fibres pass into the corpus callosum or into the fasciculus subcallosus. In the dorsal part of figs. 24 and 25 fibres to both destinations may be seen. It is very likely that the termination of commissural fibres is diffuse on the opposite side. There is, however, such a doubtful loss of cortical fibres in the uninjured hemisphere that one must suppose that here, even to a greater degree than in the Rolandic region, the commissure does not connect homologous parts. More than one preparation led me to suppose that a part of the corpus callosum serves to connect the neostriata on each side, that is the nucleus caudatus and putamen nuclei lentiformis. But I have not been able to find cell degeneration of these ganglia which would be a convincing proof of this. In analogy with the archistriatal commissure which connects the nuclei amygdalæ, and a possible commissure between the palæostriata in Meynert's commissure, such a connexion of the phylogenetically most recent parts of the striatum would not be improbable. In any case there is a considerable number of fibres in the corpus callosum which unquestionably passes from the one hemisphere to the other, the origin and ending of which we do not know with any degree of certainty. On these grounds the statement that the corpus callosum simply connects the cortex of both sides, either homotopically or heterotopically, or in both ways, must be abandoned.

The height to which the cortico-petal callosal fibres ascend in the cortex is indicated by the preparations from which figs. 19, 20, 22, 23, have been taken; in these either the short fibres are intact, or smaller proportions have disappeared than of the long ones which reach into and above Brodmann's layer IV.

I have been unable to determine with certainty from these investigations on human brains from which cells of the cortex, or from which layers, callosal fibres arise. It is certain that the giganto-pyramids of field 4 (Brodmann), in the cases where the gyrus centralis anterior was completely separated from the centro-parietal callosal radiation, have not suffered appreciably. I have had no opportunity of investigating the remaining cortical areas in cases of isolated callosal lesions with satisfactory cell-staining methods.

The cell changes discovered in the deeper cell layers in the experimental observations on the cat, rabbit and mouse, were possibly only temporary.

Various remarks have been made already concerning the physiological significance of the callosal fibres of the "parastrial" part of field 18. An attempt has been made to explain the fact that the primary visual cortex is not commissurally connected with the opposite side, while the surrounding region, which is closely associated with eye-movements, has commissural fibres. In the remaining portions of the occipital cortex the callosal ending appears to be diffuse. A relatively circumscribed termination of callosal fibres occurs in the Rolandic zone, from which compact cortico-fugal bundles—consisting of commissural and projection fibres (including the pyramidal tract)—arise. According to Mott, a direct influence of corresponding points of the "motor" cortex on each other appears to be certain, while the connexion between the gyrus centralis anterior of the one and the gyrus centralis posterior of the other side seems to be more diffuse. As already stated, the origin and ending of this connexion lies in about the same horizontal plane, both in front and behind the fissure of Rolando.

The posterior central convolution is above all a primary cortical sensory centre, and contributes in large measure to the building up and the regulation of the movements which are innervated from the gyrus centralis anterior; these motor impulses descend from the giganto-pyramids of the fifth cortical layer. Both homotopical commissural impulses from the contra-lateral anterior central convolution to the superficial layers of this motor field, and the heterotopical impulses from the same region, to the adjoining part of the posterior central convolution, may also contribute to the elaboration of the motor impulse.

The inability to follow the commissural connexions of the frontal lobes, even though they probably exist, adds to our ignorance of the functional significance of these regions and renders physiological conclusions on this part of the corpus callosum impossible.

A few clinical remarks were made in the introduction on the pathology of the corpus callosum. It is remarkable that of all the symptoms described in cases of callosal lesions very few may be ascribed, with any degree of certainty, to destruction of the commissural connexions. Perfectly isolated callosal lesions rarely, if ever, occur, and the total absence of this great commissure does not *necessarily* cause any typical symptom. I therefore neglect many intrinsically interesting communications of cases in which, in addition to other disturbances, the corpus callosum was absent, and where possibly a special symptom might be ascribed to this. It must be admitted that the symptomatology is very variable. Practically only those cases come under consideration where either an isolated, or more or less local, callosal softening existed, or in which by a softening in one hemisphere, a function was disturbed, which is not under the control of that hemisphere alone. Such disturbance, when remote influence by a tumour, &c., may be excluded, can only be explained through the commissural fibres.

In the first place my investigation offers an anatomical explanation of the well-known fact that in cases of cortical epilepsy the excitation of a motor centre in the affected hemisphere, can cross through the corpus callosum to the homologous centre in the healthy hemisphere. If the progression of the convulsions from the one side to the other is not accurately homotopical, as is indeed often the case, it may be assumed that the excitation of the centre first affected was so strong that the irritation spread directly from here to the homologous region of the opposite hemisphere.

Indirect apraxia (apraxia callosa) of the left extremities which Liepmann has described, is assumed to be due to a lesion of the commissural connexion between the left and right sensorio-motor centres. This view, put forward by Liepmann, is closely connected with his statement that the left sensorio-motor centres have a primary rôle in evoking more complicated actions in general; even the movements necessary for given action of the left limbs are innervated from the right hemisphere. The result of my anatomical investigations, that there exists a connexion between the gyrus centralis anterior and the two contra-lateral central convolutions, may assist in the explanation of the fact that this indirect apraxia itself can be considered as a "cortical" disturbance ("gliedkinetische, innervatorische Apraxie"). The movements of the left arm are then not disturbed in consequence of a deficient formulation of the "psychic plan," nor by the ineffective transmission of the "plan" to the region, whence the execution takes place finally, but by the inadequate execution of the action itself, as this depends on the adequacy of the immediately preceding intra-cortical activity; but this must not be confused with the regulating impulses from the immediate proximity, the disturbance of which produces cortical ataxia. In Case 6 only two-handed movements were disturbed, not only because these needed the co-operation of the apraxic right hand, but because the functions of the left hand were primarily affected. All remaining actions of the left hand, as far as they could be examined in the aphasic patient, were quite normal.

In addition to the complete apraxia, there was a strong disinclination to make any movement of the right hand or arm. Whether its innervation was affected by the extensive centro-parietal, or by the frontal softening, as Foerster [8] and others seem to believe possible, it is certain that the initiative of the left arm and hand was not lessened by these large lesions. There can be, in any case, no question of a unilateral "eupraxic-centre."

Finally, there is the question as to the causes of mind-blindness. A lesion of the posterior part of the corpus callosum is generally considered, at least partly, responsible for this. If this assumes that it is due to the commissural connexion between two primary visual fields (areæ striatæ) being disturbed, the view is untenable, as it is an anatomical fact that no such connexion exists. If the chief cause of mind-blindness is to be sought in a lesion of the callosal fibres, it must be of those that connect other parts of the two occipital lobes, and it is certain that fields 18 and 19 (Brodmann) receive and give rise to parastrial radiations. These regions of the cortex comprise the "visuo-psychic area" of the English authors (Bolton, Mott, Campbell). It is certain that these fields co-operate with the area striata in the higher visual functions. They are, moreover, phylogenetically more recent than field 17, and increase relatively in the higher mammals. Parallel with this the occipital callosal fibres become more abundant. The exactness of the hypothesis of Niessl v. Mayendorf, that in visual function the left hemisphere predominates over the right, and localized softenings of the pole and ventral part of the occipital lobe ("left macula centre") may cause mind-blindness, can be determined only by fuller clinical and anatomical investigations.

One will then have to reckon with the fact that the area striata has no commissural connexions.

REFERENCES.

[1] Anton und Zingerle. "Bau, Leistung und Erkrankung des menschlichen Stirnhirns," Festschrift der Grazer Universität für 1901.

[2] Ascenzi. "Una cista emorragica del corpo calloso," *Riv. di patol. nerv. e ment.*, 1908, vol. xiii, p. 1.

[3] Beevor. "On the Course of the Fibres of the Cingulum and the Posterior Parts of the Corpus Callosum and Fornix in the Marmoset Monkey," *Phil. Trans. Roy. Soc. Lond.*, 1892, B., vol. clxxxii, p. 135.

[4] Cajal, S. Ramon y. "Texture del sistema nerviosa," t. ii, pp. 845, *et seq.*

[5] Carville et Duret. *Arch. de Physiol.*, 1875, t. vii, p. 352 (cit. after Korányi).

[6] Dejerine. "Anatomie des centres nerveux," Paris, 1895.

[7] Dotto e Pusateri. "Sul decorso delle fibre del corpo calloso e del psalterium," *Riv. di patol. nerv. e ment.*, 1897, vol. ii, p. 64.

[8] Foerster, E. "Ueber Apraxia bei Balkendurchtrennung," *Monatsschr. f. Psychiat. u. Neurol.*, 1913, Bd. xxxiii, S. 493.

[9] Forel. "Gesammelte hirnanatomische Abhandlungen," München, 1907, S. 230.

[10] Gans. "Der Mikroskopische Befund des Goldsteinschen Falls von linksseitiger Apraxie," *Fol. Neurobiolog.*, 1912, Bd. vi, S. 787.

[11] Gianelli. "Softening of the Genu Corporis Callosi," *Journ. of Ment. Pathol.*, 1907, vol. viii, p. 49.

[12] Goldstein. "Beiträge zur Entwickelungsgeschichte des menschlichen Gehirns," *Anat. Anzeiger*, 1902-03, Bd. xxiii, S. 72.

[13] *Idem.* "Zur Lehre von der Motorischen-Apraxie," *Journ. f. Psychiat. u. Neurol.*, 1908.

[14] Hartmann. "Beiträge zur Apraxielehre; Fall 11," *Monatsschr. f. Psychiat. u. Neurol.*, 1907, Bd. xxi. S. 97.

[15] Henschen. "Klinische und Anatomische Beiträge zur Pathologie des Gehirns," Upsala, 1903, 1911, Bd. iv.

[16] His. "Entwicklung des menschlichen Gehirns," &c., Leipzig, 1904.

[17] Inouye. "Die Sehstörungen bei Schussverletzungen der corticalen Sehsphäre," Leipzig, 1909.

[18] Kattwinkel. "Untersuchungen über das Verhalten des Balkens nach grösseren corticalen Hirnläsionen," *Deutsche Arch. f. klin. Med.*, 1901, Bd. lxxi, S. 1.

[19] Kisaku Yoshimura. "Ueber die Beziehungen des Balkens zum Sehakt," *Pflüger's Archiv*, 1909, Bd. cxxix, S. 425.

[20] Kölliker. "Handbuch der Gewebelehre des Menschen," Leipzig, 1889-1902, 6th Aufl.

[21] Korányi. "Ueber die Folgen der Durchschneidung des Hirnbalkens," *Pflüger's Archiv*, 1890, Bd. xlvii, S. 35.

[22] Landsbergen. "Ueber Balkenmangel," *Zeitschr. f. d. ges. Neurol. u. Psychiat.*, 1912, Bd. xi, S. 515.

[23] LANGELAAN. "Development of the Large Commissures in the Human Brain," *Brain*, 1908, vol. xxxi, p. 221.

[24] LANGLEY and GRÜNBAUM. "On the Degeneration resulting from Removal of the Cerebral Cortex," &c., *Journ. of Physiol.*, 1890, vol. xi, p. 606.

[25] LENZ. "Zur Pathologie der corticalen Sehbahn," &c., Leipzig, 1909.

[26] LÉVY-VALENSI. "Le corps calleux," *Thèse de Paris*, 1910.

[27] LIEPMANN. "Die linke Hemisphäre und das Handeln," *Münch. med. Wochenschr.*, 1905, Bd. lii, S. 2322.

[28] LIEPMANN und MAAS. "Ein Fall von linksseitiger Agraphie und Aphasie bei rechtsseitiger Lähmung," *Journ. f. Psychiat. u. Neurol.*, 1907, Bd. x, S. 214.

[29] MARCHAND. "Ueber die normale Entwicklung und den Mangel des Balkens im menschlichen Gehirn," *Abhandl. d. Kön. Saechs. Ges. d. Wissensch.*, 1909, Bd. xxxi, S. 370.

[30] MARIE et GUILLAIN. "Ramollisement du genou du corps calleux," *Rev. neurol.*, 1902, t. x, p. 281.

[31] MINGAZZINI. "Klinische Beiträge zur Kenntnis der Hirntumoren," *Monatsschr. f. Psychiat. u. Neurol.*, 1906, Bd. xix, S. 442.

[32] MINKOWSKI. "Zur Physiologie der corticalen Sehsphäre," *Deutsche Zeitschr. f. Nervenheilk.*, 1911, Bd. xli, S. 109.

[33] LO MONACO. "Fisiologia dell corpo calloso," *Riv. di patol. nerv. e ment.*, 1897, vol. ii, p. 145.

[34] LO MONACO e BALDI. "Sulle degenerazioni consecutive al taglio longitudinale del corpo calloso," *Arch. di farmacol. sperimentale*, 1904, vol. cxi, p. 475.

[35] MOTT. "Report on Bilaterally Associated Movements, and on the Functional Relations of the Corpus Callosum to the Motor Cortex," *Brit. Med. Journ.*, 1890, vol. i, p. 1124.

[36] MURATOFF. "Secondäre Degeneration nach Durchschneidung des Balkens," *Neurol. Centralbl.*, 1893, Bd. xii, S. 714.

[37] *Idem.* "Secondäre Degeneration nach Zerstörung der Motorischen-Sphäre des Gehirns," &c., *Arch. f. Anat. u. Physiol.*, 1893 (Anat. Abth.), S. 99.

[38] NIESSL V. MAYENDORF. "Das Rindenzentrum der optischen Wortbilder," *Arch. f. Psychiat.*, 1908, Bd. xliii, S. 633.

[39] NISSL. "Zur Lehre der Lokalisation in der Grosshirnrinde des Kaninchens," Heidelberg, 1911.

[40] PROBST. "Ueber den Bau des vollständig balkenlosen Grosshirns," &c., *Arch. f. Psychiat.*, 1901, Bd. xxxiv, S. 709.

[41] *Idem.* "Weitere Untersuchungen über die Grosshirnfaserung," &c., *Sitzungsb. der Kais. Akad. der Wissensch.*, 1905, Bd. cxiv, Abth. iii, S. 173.

[42] RANSOM. "On Tumours of the Corpus Callosum," &c., *Brain*, 1895, vol. xviii, p. 531.

[43] SACHS, H. "Ein Beitrag zur Frage des fronto-occipitalen Associationsbundels," Verein der deutschen Irrenärzte, 1895, *Centralbl. f. Nervenheilk.*, 1896, Bd. vi, S. 30; also *Allg. Zeitschr. f. Psychiat.*, 1896, Bd. liii, S. 181.

[44] SCHNOPFHAGEN. "Die Entstehung der Windungen des Grosshirns," &c., *Jahrb. f. Psychiat.*, 1889-90, Bd. ix, S. 197.

[45] SHERRINGTON. "Experimental Note on the Movements of the Eye," *Journ. of Physiol.*, 1894-95, vol. xvii, p. 27.

[46] *Idem.* "Integrative Action of the Nervous System," London, 1906.

[47] *Idem. Journ. of Physiol.*, 1889, vol. x, p. 429.

[48] STÖCKER. "Ueber Balkenmangel im menschlichen Gehirn," *Arch. f. Psychiat.*, 1913, Bd. 1, S. 543.

[49] v. GUDDEN. "Gesammelte und hinterlassene Abhandlungen," Wiesbaden, 1889, S. 130.

[50] v. MONAKOW. "Durch Extirpation circumscripter Hirnrindenregionen bedingte Entwickelungshemmungen des Kaninchengehirns," *Arch. f. Psychiat.*, 1882, Bd. xii, S. 141.

[51] v. VALKENBURG. "Contribution à l'étude de la substance blanche occipito-temporale de l'homme," *Psychiat. en Neurol. Bl.*, 1911, Bd. xv, Bldz. 374.

[52] *Idem.* "Zur Anatomie der Projections- und Balkenstrahlung des Hinterhapptslappens sowie des Cingulums," *Monatsschr. f. Psychiat. u. Neurol.*, 1908, Bd. xxiv, S. 320.

[53] v. **Valkenburg.** "Over Apraxie," *Nederl. Tijdschr. v. Geneeskunde*, 1909, Bldz. 166.

[54] *Idem.* "The Origin of the Fibres of the Corpus Callosum and the Psalterium," *Roy. Acad. of Scien.*, Amsterdam, 1911.

[55] v. **Valkenburg** and **Mestrom.** "The Optic Centres in the Brain of an Anophthalmos," *Roy. Acad. of Scien.*, Amsterdam, May, 1913.

[56] v. **Vleuten.** "Linksseitige motorische Apraxie," *Allg. Zeitschr. f. Psychiat.*, 1907, Bd. lxiv, S. 203.

[57] **de Vries, J.** "De cellulaire bouw der grootehersenschors van de muis en de veranderingen daarin na doorsnijding van het Corpus Callosum," J. D. Groningen, 1911.

[58] **Zuckerkandl.** "Entwicklung des Balkens und des Gewölbes," *Sitzungsb. der Kais. Akad. der Wissensch.*, 1901, Bd. cx, Abth. iii, S. 233.

[59] *Idem.* "Entwicklung des Balkens," *Arbeiten. a. d. Neurol. Inst. Wien*, 1909, Bd. xvii, S. 373.

SENSORY CHANGES IN FRIEDREICH'S DISEASE.

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THE sensory changes in Friedreich's disease have been studied by several observers. Noïca, in two cases of the disease that he examined carefully, found very considerable loss to different forms of sensibility. Egger, in his investigations of "osseous sensibility," considered that this is regularly affected in Friedreich's disease. Other investigators have from time to time reported cases in which a certain amount of sensory loss was present, and cases indeed with some sensory loss have been mentioned incidentally from the time of the early differentiation of the disease from tabes dorsalis, and its occurrence is referred to in most neurological text-books.

The classical description of the disease, however, while admitting that loss to some or all forms of sensation may occur, regards it as altogether an unusual and exceptional feature, notwithstanding the fact that one of the great sensory paths of the cord is the chief site of the pathological changes that are present in the disease. A series of systematic observations, therefore, on a considerable number of cases of Friedreich's disease would seem justified, in order to see how far the classical description of the disease holds in the light of our present knowledge concerning the different forms of sensibility.

The chief aim, however, in undertaking this work has been the important question of sensory conduction in the cord, as the more recent work of Petrén, Rothmann, Head and his collaborators, and other investigators make it probable that impulses underlying the sense of position and appreciation of passive movement, the recognition of two compass-points simultaneously applied to the surface of the body, the appreciation of vibration, and the recognition of size, shape, form, and weight, and possibly of roughness and texture, are conveyed through the dorsal columns, tracts of which there is systematic degeneration in Friedreich's disease.

Most investigators now agree with the view that the dorsal columns furnish the principal pathway in the cord for the conduction of the impulses that subserve muscle-sense, meaning by that term chiefly the sense of position in space and the recognition of passive movement. Petrén concludes from his examination of cases of stab wounds involving the spinal cord that these impulses pass up the cord uncrossed in the dorsal columns and in the dorsal spino-cerebellar tracts, but the view of Head and Thompson, based on their investigation of the grouping of sensory elements in Brown-Séquard lesions, that the dorsal columns subserve the conduction of the impulses underlying the recognition of position and movement that pass to consciousness, while the spino-cerebellar tract is concerned with those impulses that are responsible for the unconscious maintenance of equilibrium, seems likely to be the more correct, and Thompson has adduced later clinical and pathological evidence from a case of Combined Degeneration to show that the sense of position and recognition of passive movement may be grossly affected by a lesion limited to the long fibres of the dorsal columns.

Head and Thompson have shown also that the recognition of compass-points simultaneously applied is dissociated in the cord from tactile sensibility, and passes up uncrossed in the dorsal columns, while Bing has brought evidence that the impulses that subserve the appreciation of vibration also pass up the homolateral side of the cord, and therefore must be conducted by the dorsal columns.

The investigations of Head and Holmes on Brown-Séquard lesions, cited in their paper, go to show that not only do the knowledge of position and passive movement, the recognition of two points, and the appreciation of vibration depend on the integrity of the dorsal columns, but that the recognition of size, shape, form, and weight, and the appreciation of consistence and texture are affected in common with these other elements of sensibility, and the impulses which underlie them would seem, therefore, also to be conducted by the dorsal tracts. Thompson also, in his case, noted that the recognition of weight was grossly affected, as well as the appreciation of position, movement and double contacts. I have had the opportunity, moreover, of seeing recently another, as yet unpublished, case of cervical Brown-Séquard lesion, studied by Dr. Holmes and Dr. Head, which goes to confirm the view that the impulses which underlie recognition of size, shape, form, weight, consistence and texture, as well as the appreciation of position, movement, simultaneous contacts and vibration, are conducted through the homolateral side of the cord.

The impulses of light touch and pressure-touch are, according to most of these observers, associated together in the cord. These impulses are conducted partly by an uncrossed path in the dorsal columns, mostly by a crossed path in the lateral columns (Petrén), or in the ventral columns (Rothmann). The localization of tactile sensibility is associated with touch and is mainly in the crossed pathway.

All impulses of whatever kind that are painful, all heat impulses and all cold, cross almost at once after a relay in the dorsal horns, and pass up the cord in the opposite lateral column, though possibly some of them pass without crossing by the lateral column of the same side.

Systemic degenerations of the dorsal columns are not numerous. Tabes dorsalis, it is generally recognized, is, at least predominantly, a disease of the dorsal roots. In Combined Degeneration the process is probably not a true system degeneration but a funicular myelitis (Nonne). In Friedreich's disease, however, we have a condition which is usually regarded as essentially a systemic degeneration of the dorsal columns, even although the pathological changes are not limited to them.

The changes in the dorsal column tracts are the most constant and most pronounced feature of the pathological anatomy of the disease, and are present in all cases. In the sacral and lumbar regions these tracts may be almost entirely degenerated, but higher in the cord the degeneration in the column as a whole is not so marked. In the dorsal and cervical regions, the root-entry zone seems considerably less affected than the rest of the column ; and the cornu-commissural zone, the areas immediately next the grey matter of the dorsal horns, and Lissauer's tract may be scarcely at all affected. The degeneration in the other parts of the column, however, remains very severe throughout the whole cord. The long and medium fibres of the dorsal columns are therefore the ones chiefly affected, and the affection of these may be so intense that scarcely a fibre may remain visible in cross-section.

In the other tracts involved in the disease, the pyramidal and the spino-cerebellar, the degenerative changes are rarely so great as in the dorsal columns. The affection of the pyramidal tracts is most intense in the sacral and lumbar regions and diminishes as we pass up the cord, though in some cases it may be traced as far the pons or the lower part of the crus. The degeneration in the spino-cerebellar tracts, on the other hand, increases in extent and degree, from below upwards and becomes most pronounced in the higher cervical segments.

As contrasted with the great affection of the fibres in these different tracts, and especially in the dorsal columns, the changes in the cells are not so frequent or so pronounced except, perhaps, in Clarke's column. In some cases the spinal ganglion-cells are slightly atrophied and the dorsal spinal roots and even the peripheral nerves may be involved. There is, however, no sufficient reason to consider that the affection of the dorsal columns is secondary to a primary degeneration of the ganglion-cells or of the dorsal roots, for the changes in the roots are not nearly so definite, so frequent, or so intense as in the dorsal columns, and the affection of the ganglion-cells is slight and inconstant.

The widespread nature of the pathological changes in this disease and its variable incidence on different systems of fibres in the cord are in harmony with the view that it is a true systemic degeneration of the long spinal tracts, and especially of the dorsal column system. But even if the degeneration in the dorsal columns be regarded, not as a primary systemic one, but as due to an elective or chance degeneration in the dorsal roots, the existence of profound changes in these columns is by far the most outstanding feature of the pathology, and we should expect, therefore, to find in Friedreich's disease those forms of sensibility disturbed which have been assigned to the dorsal columns, and disturbed in proportion to the intensity of the dorsal column affection.

For the purpose of investigating this, I have examined systematically twenty cases of Friedreich's disease. These were obtained from the practice of the National Hospital, Queen Square, and I must here express my indebtedness to the medical staff for permission to publish the results of my examination. To Dr. Gordon Holmes I am very specially indebted also, for constant help and advice throughout the whole investigation. All the patients examined presented the usual signs of Friedreich's disease, the skeletal deformities, the absent deep reflexes, the extensor plantar responses, the nystagmus, and the ataxia so characteristic of the disease.

The methods used in examining these patients were mainly those employed by Head and Holmes in their work on sensory changes in cerebral lesions, in as far as these were applicable. They had to be modified somewhat, because the symptoms in Friedreich's disease were of course bilateral, and, therefore, there was no sound side which could be used as a standard of comparison to estimate the amount of loss present as in Head and Holmes' work, where the disturbance was unilateral.

Tactile sensibility was tested by means of light touches with jeweller's cotton-wool. It was not considered necessary or advisable to employ more elaborate methods, or to attempt to obtain thresholds by means of von Frey's hairs. It was found that just as satisfactory results could be got by means of the light cotton-wool as by von Frey's hairs in the cases in which both were used and the results compared.

Pressure-touch was examined by means of contacts with the observer's finger or other blunt object. The localization of tactile sensibility was tested usually by Head and Holmes' modification of Henri's method. Cutaneous sensibility to pain was examined by means of a pin-prick, and the appreciation of differences of temperature by means of tubes of hot and cold water of moderate degrees of temperature. Pressure-pain was tested by noting the amount of pressure on the subcutaneous structures necessary to produce discomfort. Cattell's algometer was used in many instances to test it, but was found so unsuitable for the character of the cases studied that its use was abandoned.

The sense of posture was tested in the usual way by making the patient indicate by description or by imitation with the homologous limb the position in which any segment of the limb that was being examined was placed; or by making him point with one index-finger to the position in space of some fixed point, such as the tip of the opposite index-finger, or the heel or the toe of the limb under examination. The latter method was naturally untrustworthy in cases in which there was either much ataxia or much loss of the sense of posture in the arms.

The appreciation of passive movement was examined in the ordinary way also by moving any segment of a limb slowly and uniformly through an angle sufficient to allow the patient to appreciate the movement and recognize its direction. It is, of course, important that the necessary pressure made by the examiner in holding the limb should be varied as little as possible, lest the patient should become aware of the movement by adventitious sensations. Where the loss is considerable this rough clinical method is sufficient, though, of course, due weight must be given to the intelligence of the patient, to the readiness with which he can respond, and to his power of description. When the loss is slight, however, it is essential to measure by some such instrument as that employed by Head and Holmes the number of degrees through which a segment of the limb must be moved in order to evoke appreciation of movement and its direction, the figures thus obtained being compared with a corresponding set of readings from a control patient or with the average normal.

The recognition of two points applied simultaneously to the skin was tested usually over the palms of the hands, the palmar surface of the tips of the fingers, the soles of the feet, and in some cases the surface of the forearm, of the leg, and of the thigh. In recording the patient's answer, ten double touches and ten single touches on each area were charted, according to the formula used by Head and Rivers, and, in order to compare the results with the normal, the maximum threshold, that is the smallest distance of the points apart necessary for a complete series of correct answers, was determined in each place.

In testing the appreciation of vibration a large tuning-fork (C.° 128) was used. The fork was made to vibrate strongly, and was then placed on some definite part of the patient's limb, and if he appreciated the vibration he was told to say immediately when he ceased to feel it. The fork was then transferred to the corresponding part of the limb of a control patient, and he was told to say immediately it ceased to vibrate. This was repeated several times, and the results were tabulated.

In order to eliminate as far as possible the factor of physiological fatigue which might have accounted for the control's appreciation of the vibration after the patient had ceased to feel it, a set of readings was taken in the reverse order, the fork being placed first on the control and then on the patient. These double readings could then be compared, and, if necessary, added together. Some precaution of this sort in testing vibration is the more necessary for, as Neutra has pointed out, even in the normal individual, vibrations may be appreciated on the one limb after they have apparently ceased on the corresponding point of the opposite limb.

The recognition of form, shape, size, and weight was tested by using standard objects, such as those introduced by Head and Holmes. The ability to recognize form—that is, three dimensional objects — and shape—or two dimensional objects—is evidently not measurable, but a threshold to the recognition of size and weight can be obtained by ascertaining the relative difference that can be recognized in the size or weight of similarly shaped objects applied successively. The appreciation of roughness was tested with Graham-Brown's æsthesiometer.

Owing to the bilateral character of the symptoms, it was found necessary to introduce, especially in the cases where the loss was of moderate degree only, some method of control or some normal standard. It was found useful, therefore, to examine, side by side with each patient, a normal person, or one normal as far as sensation was concerned, of about the same age and intelligence as the patient, and to compare the different results of the examination as found in the patient with those found in the control. It was considered important, in order to strike a normal average, not always to use the same control, and in most instances, therefore, a different control was used for each patient.

In all those forms of sensibility which were measurable, such as the appreciation of movement, the recognition of compass-points, the appreciation of vibration, and the recognition of differences of size and weight, measurements over a series of readings in the patient were compared with measurements in the control. In this way slighter degrees of loss could be rendered apparent, and the subjective element on the examiner's part eliminated as far as possible.

It must be recognized, however, that although measurement may seem to make the tests and conclusions drawn from them more exact, there is considerable danger of error and confusion if proper precautions are not adopted. Measurements have a relative value only, as they depend largely on the intelligence of the patient and the readiness with which he responds. This difficulty can be obviated, however, by the examination of a considerable number of patients and the employment of controls of the same social status, education, and intelligence as the patient. It is obviously impossible to attain accurate results in such an investigation as this if the measurable defects are compared only with such an average as may be obtained in a psychological laboratory.

The following case will illustrate the methods adopted in the examination of the patients for this paper, and will show also the character of the sensory loss that is found in a somewhat advanced stage of Friedreich's disease.

A. H., aged 23, is the eldest of a family of four children; one of his sisters, aged 16, has Friedreich's disease.

When he was 7 years old his parents first noticed that he was unsteady in his walking and seemed unable to stand properly. He was taken to hospital and was admitted for about six weeks. The unsteadiness in his gait, however, continued, and his subsequent history indeed was mainly one of gradually increasing reeling and staggering with, at times, apparently acute increase following intercurrent illness. At length, a few years ago, he became unable to walk at all, and now he can barely stand even with much support. His arms and his hands, he says, began to be unsteady in their movements soon after his legs were affected, and his speech, he thinks, gradually became jerky and difficult after an illness at about the age of 16. Except for the intercurrent periods of illness, after which his legs would always seem worse, his general health has been fairly good.

He is a thin, pale, rather undersized lad, somewhat sleepy looking, but quite intelligent. On examination he shows all the usual signs of Friedreich's disease, the nystagmus, the explosive speech, marked scoliosis, much pes cavus, absent deep reflexes, and extensor plantar responses. All his limbs are very hypotonic and there is much inco-ordination and over-action in the movements of his arms and legs. His legs also are weak and slightly wasted. His back is weak and the muscles there, too, lack tone, so that he is very unsteady when sitting up unless he has some support to lean against.

His sensory loss is very considerable.

In the upper extremities he could appreciate all light cotton-wool touches quite well, except on the distal parts of the back of the fingers and on the palms of the hands, that is on hairless parts. Over these areas there seemed to be some hypoæsthesia. On the trunk his responses to cotton-wool touches were good. On the lower extremities he seemed to appreciate light touches quite well above the knees, but on the legs relatively heavy touches with cotton-wool were often necessary, and on his feet he missed many contacts, even when the wisp of wool was drawn to and fro. When some patches were shaved on the legs and thighs it was found that he could usually appreciate light touches even then, except on the lower parts of the legs, where he missed a considerable number. It seemed, therefore, that he had some tactile loss on his feet and the lower parts of his legs, the upper limit of which shaded gradually into the normal areas higher on the limbs.

Light pressure-touches with the finger were appreciated quite well everywhere on the upper and lower extremities and on the trunk. There was no distal loss whatever on the limbs to this form of stimulus.

To pin-prick no definite loss was noted anywhere. He seemed to appreciate the point of the pin well, even over the legs and the feet, and he admitted no difference in sharpness when areas towards the distal extremity of the limbs were compared with areas higher up. Pressure-pain readings taken with the algometer were undoubtedly high, especially on his hands, but making allowance for the variability of the results obtainable with this instrument, I could not say there was definite pathological loss.

Tubes of hot and cold water of very moderate degrees of difference of temperature were always appreciated quite correctly, even over the distal parts of the legs. His answers to these, as to the pin-prick, were ready and accurate.

In localizing any point stimulated on the surface of the body or limbs he made a few mistakes, but the errors were not definitely outside physiological limits.

In the upper extremities there was very great loss of the recognition of position in the fingers of both hands. When asked he frequently said he had no idea of the position in which a finger was, and when told to imitate the position of the fingers of one hand with those of the other, he was often quite wrong. He had very great difficulty also in finding the position of one finger with the other when his eyes were shut, very much more than his ataxia would account for. As his arms lay by his side the fingers and even the forearm tended to move about irregularly, as is common in limbs in which there is severe loss of the sense of position.

Passive movement was very poorly and very slowly recognized in the fingers, at the wrists, and even, though in less degree, at the elbows on both sides. A large range of movement could be passed through before he recognized that any movement had taken place; he did not, for instance, recognize passive movements of his right forefinger until it was moved through a much greater angle than normal, and when he did recognize that a movement had taken place he frequently could not tell its direction. This is well shown by the following readings of the angles subtended by the minimum movements of the forefinger necessary to evoke recognition in his case and in the case of a control patient:—

Control

Extension	1°		1°		1°	<1°	<1°	
Flexion		1°		1°				<1°

Patient

Extension	25° nil.	25° nil.				27°.	40°?			30° nil.	
Flexion			20°.	30° nil.	25°.			30°.	25°.		25°.

In these readings the "nil" placed after the number of degrees means that, though at this number of degrees he recognized that a movement had taken place, he could not describe its direction; a query means that he was in doubt.

In the lower extremities also there was very gross loss of the sense of position, and he had really very little idea of the position his foot occupied in space. He could recognize that his great toe on either foot was being touched when the examiner grasped it, but could not tell whether it had been moved or not, and could not describe what position it was in at any given moment. His loss of recognition of position and of appreciation of passive movement at the ankle as well as in the toes seemed complete. At the knees the recognition of position and of passive movement was very poor, while at the hips the loss was very much less.

The range of passive movement at his knee necessary to evoke recognition and that in the case of a control gave the following results:—

Control

Extension	<1°		<1°				<1°			1°
Flexion		<1°		1°	<1°	<1°		<1°	1°	

Patient

Extension	35° nil.		23°.		35° nil.			28°.	35° nil.	
Flexion		21°.		17°.		21°.	19°.			15°.

His power of recognizing two simultaneous contacts was grossly defective. On the ulnar border of both palms he gave wrong answers with the compass-points even 7 cm. apart, whereas the control gave a correct reading quite readily with the points at less than 1 cm. apart. The readings at 7 cm. on the right hand were:—

1	XII		I		I		XXII		I	
2		XXX		I		XX		XIX		I

Over the palmar surface of the tip of the middle-finger of his left hand, where a normal individual will recognize simultaneous contacts with compass-points 2 mm. apart, he was grossly wrong when the compass-points were 2 cm. apart, the readings being

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1|  XI  XIIXX   I XX
-|--------------------
2|II  XX     IXX I  IX
```

and over his forearm he made many errors with the compass-points 15 cm. apart. The loss was so great, therefore, that it was impossible over the hands to get a maximum threshold. Over the lower extremities also the loss was profound. With the compass-points at a distance of 12 cm. from each other on the sole the errors were so numerous that he was obviously guessing. The reading at this distance was

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1| II  IXXII  X XX
-|--------------------
2|X  ID     XX I  XIXI
```

His foot was so deformed that this distance extended from the heel to the ball of the great toe, so that here too it was impossible to get a threshold for correct answers. The control gave correct answers readily over the sole with the compass-points 3 cm. apart.

In the feet and up to the knees the appreciation of vibration was extremely poor. On different parts of the left foot, he could not appreciate even the strongest vibration and on the right he could recognize it very slightly. On the left leg and up to the left anterior superior spine of the ilium he failed to appreciate the vibrating fork at all, while on the right it evoked a slight sensation only. Over the ribs on both sides he could recognize it, while on the hands again and the wrists and lower parts of the forearm on both sides there was a very large amount of loss.

When his appreciation of form was being tested, his answers were slow and were frequently wrong, even though the objects had all been shown to him before the examination began. Thus he made four mistakes out of twelve trials with the right hand, and seven out of twelve with the left. When he was given ordinary objects such as a knife or a coin that he had not been shown before the examination began, he fumbled with them and usually failed to name them.

He was also unable to recognise two dimensional shapes on his palms, usually replying that "he didn't know," or "he couldn't feel the shape of it," or else answering wrongly and hesitatingly.

His appreciation of differences in size was less disturbed, but showed definite defect. He nearly always recognized correctly a difference of 1 cm. in the diameter of two discs 3 and 4 cm. across, and sometimes distinguished between discs 3·5 and 4 cm. in diameter.

His appreciation of differences in weight showed definite defect. When 100 and 200 grm., or even 50 and 200 were compared on his supported hand he was as often wrong as right, and even with 100 and 200 grm. tested on his unsupported hand half his answers were wrong. He was, however, able to distinguish readily between 500 grm. and 100.

His threshold to roughness measured with the Graham-Brown æsthesiometer was a little high on the palm and sole, but not grossly so.

The sensory loss found in this patient then, briefly, includes slight tactile loss over the distal parts of the upper and lower extremities with preservation of the cutaneous sensibility to pain, temperature, and pressure-touch; gross loss of the sense of position and of the recognition of passive movement in the distal joints especially, in all the limbs, and severe disturbance of the appreciation of vibration and of the power of recognizing simultaneous contacts on the distal parts of the upper and lower extremities; with some defect or even marked loss in the recognition of form, shape, size and weight in both hands. That is to say, the sensory loss falls very lightly on the sensibilities of touch, pain, and temperature, and very heavily on the elements of local and spatial discrimination, those elements, in a word, whose spinal path has been considered to lie in the dorsal columns.

A sensory loss similar in character to this would seem to occur frequently in Friedreich's disease. Out of the twenty patients examined for this paper, I found it present definitely in eighteen. It was not always so intense as in this patient, while in some others it was even more evident. The case I have described is obviously an advanced one, and I have purposely described it in order that the peculiar character of the sensory loss might be more easily seen. The patients examined, however, represented all stages of the disease from the early to the late, and, in like manner, the sensory loss they exhibited is of all degrees of intensity and varies from very slight to very great, but wherever it was present it always fell most heavily on those elements of sensibility chiefly affected in the case just described.

In the early stages of Friedreich's disease no definite sensory loss may be demonstrable. One of my patients was a little girl, aged 7, who was a member of a family in which Friedreich's disease occurred, but the only signs of it she presented were absent knee-jerks and slight uncertainty of movement hardly more than a choreiform restlessness of the head and shoulders. She had no obvious sensory loss. In other early cases, the sensory loss may be very slight and usually, indeed, those forms of sensibility that were least affected in the advanced cases were intact in the early ones. Amongst all the advanced cases the loss was easily demonstrated and was invariably profound and striking.

While the sensory loss, generally speaking, is in proportion to the stage of the disease, in many cases there is no correspondence between the motor disability and the amount of sensory loss. In some cases the loss is much greater than the symptoms would lead one to expect, in other cases it is much less.

In some patients amongst those whom I examined, the affection of certain of the elements of sensation, especially of the sense of position, and the recognition of simultaneous contacts and of vibration was pronounced, and yet the ataxia was very moderate. These seem to be cases that progress very slowly, and years after the onset, when the disease is undoubtedly advanced, the disability seems paretic rather than ataxic. If we could assume that those elements of sensibility affected can be assigned to the dorsal columns, we might suppose that the dorsal column degeneration had far outstripped that of the cerebellar tracts, and that the chief brunt of the disease had fallen on them, and we know that the pathological anatomy of Friedreich's disease does afford us examples that would agree with such reasoning.

On the other hand, there are patients in whom the ataxia is much more marked, even in an early stage. These patients may be unable to get across a room without the help of the furniture, and yet the sensory loss, though quite definite, is far from being so advanced as the greater disability of the patient might have led us to expect. In these patients we must suppose an earlier and greater incidence of the disease on the cerebellar tracts. Between these two extremes all varieties are to be found, according to the relatively greater involvement of the one or the other of these systems.

It must not be assumed that the sensory loss is a more or less negligible factor in the production of symptoms. A slowly increasing loss of postural sensibility may, we know, admit of much voluntary compensation, but as the disability of the patient becomes more advanced, it is undeniable that the loss of sensibility tends to play an important part in the production of his final condition, just as it does in tabes dorsalis. I have found no patient, so advanced as to be unable to walk, in whom the sensory loss was not gross in character.

Generally speaking, the different elements of sensibility affected in any given case were affected in the same relative degree as in the case described; for example, amongst the elements of cutaneous sensibility, if these were involved, touch was usually more disturbed than cutaneous pain or thermal sensibility, while the sense of position, the recognition of simultaneous contacts and the appreciation of vibration were more affected than the appreciation of form, shape, size and weight, and if the former group was only slightly affected then the latter might be intact.

In all cases the sensory loss occurs earlier and affects the lower extremities much more than the upper. It is almost invariably distal in type, and although not infrequently one limb may show a greater loss of the same form of sensibility than its fellow, it is more or less symmetrical on the two sides.

The peculiar character of the loss that occurs will be seen more readily, however, if we analyse the disturbance of the different elements of sensibility and see with what frequency and to what extent they are, as a rule, affected.

Touch, pain, temperature.—The elements of cutaneous sensibility that we have to consider are light touch, light pressure-touch, cutaneous pain, recognition of heat and cold, and the localization of a point stimulated. It is at once obvious on looking over the results of the examination of a number of cases that these elements of sensibility are very much more disturbed in the lower extremities than in the upper. It will be more satisfactory, therefore, to consider their affection in the upper limbs and in the lower separately. On the trunk they were only very occasionally disturbed, the loss in the lower limbs having apparently spread upwards.

In the upper extremities many patients, perhaps the majority, show no affection of any of these forms of sensibility. In examining some patients we may get the impression that there is possibly a slight blunting of acuity in the recognition of cotton-wool contacts, of pin-pricks, or even occasionally of heat and cold, towards the periphery of the limb, but no definite loss can be demonstrated; it must be borne in mind that in many cases of Friedreich's disease the extremities are cold, bluish and congested, that is, are in that condition in which cutaneous sensibility is low even in the normal individual.

In a certain number of cases, however, as in the patient whose examination I have quoted in full, the blunting of acuity towards the distal parts of the upper limbs amounted to a slight, but definite, loss. Such tactile loss was present in five of the twenty patients; and two of these patients also had slight loss to cutaneous pain, and to heat and cold. None of them showed loss to pressure-touch, or inability to localize a point touched.

The tactile loss was limited in some of the patients to the hand, in some it passed up on the forearm, in one or two it was as high as the elbow, or even higher. It was never intense and had no sharp upper limit, but shaded off gradually into the normal part above. The pain and thermal loss, where these occurred, were similar in character and distribution to the tactile disturbance; in one of the patients, however, there seemed a slight general diminution of response to pin-prick all over the body.

It was usually in rather advanced, but not necessarily bedridden patients, that this cutaneous loss was present in the upper extremities, and it was always accompanied by much greater disorder of cutaneous sensibility in the lower limbs. Many advanced cases, however, had no definite loss in the upper limbs, a circumstance that, as will be seen, was of considerable advantage in testing other forms of sensibility, such as the recognition of simultaneous contacts which require normal tactility.

Over the lower extremities, on the other hand, a considerable number of patients had more or less severe loss of tactile sensibility. Light touch was affected in fourteen of the twenty cases. This loss was always more intense than any tactile disturbance that might be present in the upper extremities, but like the latter it was distal in its distribution over the limbs and had no sharp upper limit. In some patients it was present only over the feet, in others, it extended over the legs more or less, in others again, it was present above the knee on the thighs, and occasionally it extended to the trunk. As a rule, the more advanced the disease, the higher the upper limit of the loss extended, while the more distal areas became more deeply affected, and in some advanced cases there was almost complete tactile loss over the feet or even up to the knees.

As the appreciation of light touch diminished, pressure-touch became affected also and in not a few advanced cases, with more or less complete loss of light touch over the feet and partial loss up perhaps to the knees or higher, pressure-touch was much impaired over the feet and half way up the legs.

In the lower extremities the sensibility to pain and also that to heat and cold were, like that to touch, much more frequently affected than in the upper limbs. They were both affected with about equal frequency and were never affected without some disturbance of touch. About half the patients showed loss of varying severity. It was usually of the same distal type as the tactile loss, but less severe, and in some cases its upper limit was perhaps not so high.

The localization of a point touched was never definitely affected over the lower extremities except where there was loss of tactile sensibility.

There was never disturbance of touch, pain or temperature in the lower limbs without affection of several or all of the spatial elements of sensibility. Over the lower extremities, indeed, the cutaneous loss tended usually to increase in severity and extent as the disturbance of the power of recognising posture and vibration increased, and it was therefore more or less in proportion to either the duration of the disease or the amount of the disability present. It was not, therefore, quite so irregular and variable in its occurrence as in the upper extremities, where frequently quite advanced cases showed no affection of tactile, painful or thermal sensibility. It must be mentioned again, however, that the feet, even more than the hands, in Friedreich's disease are often bluish and cold, to such an extent as to account for much lowering of cutaneous sensibility.

In no instance did I find in either the upper or the lower extremity any cutaneous loss definitely of a root distribution. Cases have been reported occasionally, however, in which the cutaneous loss is of very unusual situation. One case recorded by Ormerod showed a complete analgesia of mask-like appearance over the face and shoulder-strap area, with a hypoalgesia over the whole body, and some areas of complete analgesia on the legs, that somewhat suggested a root distribution: Another patient reported by Jumentié and Chenet had a cutaneous loss that seemed to indicate possibly a root or peripheral nerve origin. Such distribution of sensory disturbance, frequent enough in tabes dorsalis, seems to be rare in Friedreich's disease.

Subjective changes in sensibility were rarely complained of by the patients. One patient, however, with considerable distal loss on examination in the lower extremities, complained that the application of the two points of a compass to the sole of her foot felt as if something were being drawn along the sole, a phenomenon sometimes noticed in cases of tabes dorsalis also; another complained that the vibrating tuning-fork felt hot on the sole of her foot. Frequently in testing with compass-points over the hand or the sole in patients with considerable loss, it seemed as if the sensation persisted longer than in the normal individual.

Sense of position.—The appreciation of posture and the recognition of passive movement were affected in nearly all cases. In only three of the twenty patients examined was the loss indefinite or negligible. In the advanced stages of the disease the patient was unable to describe or imitate accurately the position of his lower limbs in space, and was usually quite unaware of the relative position of their distal segments. There was invariably less disturbance in the upper limbs; the patient frequently, however, could not indicate accurately by description or imitation the position of his fingers or thumbs, and in some cases, indeed, the appreciation of posture was completely absent in these segments.

In earlier stages of the disease the diminution in the appreciation of posture was less pronounced, or was demonstrable only in the distal segments or in the lower limbs alone.

As the disturbances of the appreciation of position and the recognition of passive movements were always closely parallel, the exact extent of the affection could be more easily determined by the examination of the latter, and especially by the measurement of the smallest range of movement necessary at any joint to evoke appreciation or recognition of its direction. In one patient, for example, who had symptoms for six years, and in whom the disease had reached a stage in which gait was very unsteady and the movements of the upper limbs were badly co-ordinated, the smallest appreciable passive movements of the forefinger and those of the forefinger of a control examined alongside him subtended the following angles.

Control

Extension	1°	1°			<1°	<1°			
Flexion			<1°	1°			1°	1°	1°

Patient

Extension	$12^{\circ\times}$		25°	$20^{\circ\times}$	$40^{\circ?}$			30°	
Flexion		26°				$26^{\circ?}$	15°		27°

In every instance the control could describe the direction of the movement correctly; where the figures are marked with a cross or a query, the patient was either wrong in describing the direction or was uncertain.

In many cases the disturbance was so obvious that measurement was unnecessary, while in other earlier cases it was only by the comparison of readings taken from the affected and the normal that the diminution of sensibility could be definitely determined.

For instance, one of the patients has complained of slight symptoms for three years, and is now a little unsteady on her legs, but can use her hands well enough to work every day in a chocolate factory. The loss of appreciation of position in the great toes is quite definite, while readings of passive movements of her left forefinger gave the following result:—

Extension	14°	13°				8°		10°	9°	
Flexion			15°	12°	10°		10°			12°

At the other extreme are patients at whose wrists or knees a full range of movements may be carried out without the patient's recognizing, unless by vision, that any movement has taken place.

The distal segments are the first affected, and some disturbance can be demonstrated in the great toe, the thumb, or the fingers, even in the early stages of the disease; but as the disease advances the more proximal segments are gradually affected, though in a few cases with very pronounced defect, amounting almost to complete loss at the great toe, there was very little demonstrable loss at the knee. In these patients the symptoms progress very slowly and they remain able to walk fairly well for a long time.

The relation between the amount of loss present in the upper and in the lower extremities varied considerably in different patients, although it was always greater in the lower limbs. In some early cases the difference was slight, in others it was profound. A complete loss at the toes usually occurred in a much earlier stage of the disease than at the fingers, and a grossly wrong reading at the knee-joint could not infrequently be obtained, while it was much less common at the elbow.

The loss was generally more or less symmetrical on the two sides, but it was not uncommon to find slight differences between the corresponding joints on opposite limbs. Such differences occur all through the examination of all the forms of sensibility in Friedreich's disease, but are never at all pronounced.

In testing patients with any marked disturbance it was noticed repeatedly that the patient was able to recognize that a movement had taken place before he could distinguish its direction. This is merely an exaggeration of what occurs in the normal individual, in whom, however, the interval between the recognition of the movement and its direction is so small as to be negligible. From the consideration of some instances of early loss at certain joints, however, it seemed probable that the initial disturbance might be either an inability to decide the direction of movements that were recognized or that a movement and its direction were simultaneously recognized, but only when of a larger range than was required in the normal; that is to say, either the sense of position or the recognition of passive movement might seem to be first at fault.

The compass-test.—The examination by means of compass-points is an easy test to carry out, because of its precision and because of the ease with which it can be recorded, features which made it an extremely satisfactory test in the examination of some of the early cases.

It was usually tested only on the distal segments of the limbs, but in some cases higher up over the forearms, legs, and even thighs. The necessity of establishing normal thresholds for so many different parts of the body restricted the use of the test on the proximal segments of the limbs and on the trunk, and the examination of the distal parts of the limbs was quite sufficient in most of the cases to demonstrate loss to this form of sensibility.

In all but the very earliest cases some disturbance was found. This occurred roughly with about the same frequency as did loss of the sense of position, and, like the latter, it varied very much in different patients, but seemed to show a gradual progression from slight defect in the early stages of the disease to gross loss in the more advanced stages. For instance, while most normal individuals can distinguish two points readily at 1 cm. apart on the palm, an early case of Friedreich's disease may give a poor reading at this distance, and may require the points to be 2 or 3 cm. apart before a series of correct answers is possible; while an advanced case may show such great loss that the two points cannot be distinguished as such when they stretch the whole length of the palm.

One patient in a comparatively early stage of the disease gave the following readings on the left palm with the points at 4 cm. apart:—

$$\begin{array}{c|l} 1 & \text{\quad I \ I \ II \qquad II \ II \qquad\quad II} \\ \hline 2 & \text{IX \ X \ I \ \ IIXI \ \ I \ \ IIXXI} \end{array}$$

while another very advanced case gave the following at 6·5 cm. on the palm:—

$$\begin{array}{c|l} 1 & \text{\quad X \ X \qquad X \qquad XXX \ X \ I \ I \ \ I} \\ \hline 2 & \text{X \ X \ \ XX \ \ XX \qquad\quad X \ \ X \ X \ I} \end{array}$$

and on the palmar surface of the tip of the middle-finger, a part that in the normal individual is very sensitive, he gave the following grossly wrong reading at 2 cm.:—

$$\begin{array}{c|l} 1 & \text{\quad II \qquad\qquad XII \qquad III \qquad II} \\ \hline 2 & \text{X \quad XXXX \qquad XX \qquad XX \quad X} \end{array}$$

The errors to the application of one point in the top line of these readings do not mean that the patient is an unsatisfactory witness, but rather, as Head and Sherren have pointed out, that we are approaching his threshold for correct discrimination.

Between the slight loss in the earlier cases and the gross affection in the advanced, various degrees of loss may be demonstrated according to the stage of the disease.

While the appreciation of simultaneous contacts and the knowledge of position were affected with more or less the same frequency, they were affected also with about the same relative intensity in the different stages of the disease. It was found repeatedly that a moderate or a gross loss of the one form of sensation was present side by side with a parallel loss of the other. Occasionally, however, the loss of position might be slight, while the failure to recognize simultaneous contacts was quite marked. Less frequently again, it happened that the loss of position seemed relatively a little greater than the loss in appreciation of double contacts.

Like the loss of the sense of position, the defect in appreciating double contacts is always greater in the lower extremities than in the upper, and like it too it is usually more or less symmetrical on the two sides of the body. The tactile loss present in the lower extremities frequently interfered very considerably in the examination with compasses. In such patients the disease is usually so advanced that much error is found over the upper extremities and in the proximal portions of the lower limbs where the tactile loss is either absent or very slight.

I have observed, however, cases in which there was no demonstrable disturbance of tactile sensibility or, at the most, only a slight hypoæsthesia on the distal segments of the lower extremities, in which, nevertheless, the appreciation of two contacts was profoundly affected and grossly out of proportion to the tactile disturbance. Not only, therefore, could loss to compass-points be demonstrated in almost every case in regions in which there was no tactile disturbance, but where slight tactile loss existed the failure to appreciate double contacts was out of all proportion greater and evidently independent of it. These observations agree with the important conclusion which has been already established by the examination of clinical cases in which there is a dissociation of certain elements of sensibility, that the accuracy of the recognition of two points (that is, Weber's test) is not a measure of tactile sensibility and may be lost apart from it.

Vibration.—The appreciation of vibration was frequently and often very considerably affected. In one patient already mentioned, in whom all qualities of sensation were intact, there was of course no loss to vibration. In three others the loss was doubtful; though in each there was an apparent diminution according to actual measurement and comparison with the controls employed, the difference between the patient and the control over a series of readings was within the limits of physiological difference between two normal individuals of the same intelligence as the patients. In all the patients except these, the loss to vibration was beyond doubt, and in many cases was very pronounced.

Not only patients in the advanced stages of the disease, but many even of those able to get about quite well, may show a very marked diminution in the appreciation of vibration. In more than half of the patients the loss over some part of the body was so great that measurements were unnecessary; on certain areas the vibration was not appreciated at all.

The following example will serve to illustrate the degree of loss that may be present in a moderately early stage of the disease. One patient has had symptoms of Friedreich's disease for about four years and is now a little ataxic, but can walk fairly well. She could not appreciate the strongest vibrations of a fork on her left foot and leg, while on the right leg she could do so for about one-third as long only as the control.

Like the loss of other forms of sensibility, the diminution in the appreciation of vibration is often asymmetrical. The difference between the two sides may be recognized by the patient, who may say, "Oh, I feel it more on that side," or "it's quite different there."

In the earlier stages of the disease the loss of appreciation of vibration was always greater on the lower extremities than on the upper. As the disease advances the loss increases in the upper extremities, and may finally, in very advanced cases, be almost complete in both upper and lower limbs.

The systematic examination of a number of cases, however, shows that the diminished appreciation of vibration is not confined to the limbs, and though it is generally greater in the distal than in the proximal segments of the limb cannot be described as a distal loss in the sense in which this term was used, for example, with regard to tactile hypoæsthesia. As the disease advances, the disturbance tends to spread from the legs over the trunk, and, while in an early case there may be only some diminution in the feet, in an advanced case the loss may reach as high as the clavicles. Usually it diminishes gradually in severity from the feet upwards, and may be more pronounced over the ilium than over the hand. It would seem, therefore, that if the impulses underlying the appreciation of vibration are conveyed by the fibres of the dorsal columns, sensibility thereto is lost first in the areas that send impulses upward through the longest fibres of these columns, and the affection gradually and successively involves the fibres according to their length.

The disturbance in the appreciation of vibration frequently, therefore, seems more diffuse and widespread over the body than the defect in the recognition of posture or in the appreciation of double contacts. Occasionally, however, the appreciation of vibration was less affected than these other two; and, in general, it must be admitted that though in different patients one or other of these forms of sensation may appear the more affected, as far as we can compare such very different qualities the relative intensity of the loss of each is roughly parallel. All three show the same bilateral variations and the same tendency to the earlier and greater incidence of the loss on the lower limbs.

Form.—The recognition of form, or three-dimensional shape, was much less affected than the sense of position and the appreciation of simultaneous contacts and of vibration. It must be remembered, however, that this test could be applied in the upper extremities only where the general intensity of sensory loss was slight and much less than in the lower limbs. Further, the recognition of form is a very complex quality and depends on the cortical elaboration of impulses which pass along several paths. Moreover, the test as used in these observations is a qualitative one and could not be varied.

It was examined in seventeen of the twenty patients only. Of these ten replied readily, and named the test objects correctly; two answered slowly, fumbled the objects considerably in their hands, but named them correctly in the end; three answered slowly and made occasional mistakes, while two made frequent mistakes, and seemed to show quite definite or even gross loss in recognizing the form of the different objects.

Notwithstanding its much less frequent occurrence, the defect in the appreciation of form would seem to be more associated with the disturbance of the sense of position, the recognition of double contacts, and the appreciation of vibration than with tectile loss. In the two patients that answered very badly, tactile sensibility in the upper extremity was very slightly affected in one, and not at all in the other; and in the five that answered slowly and uncertainly, touch was never more than slightly affected in the upper extremities. The sense of position, recognition of double contacts, and appreciation of vibration, on the other hand, were very grossly affected in the two definitely marked cases, and were more or less seriously affected in the five cases of slighter loss. It would seem, therefore, that the recognition of form may be lost independently of tactile sensibility, but that its loss does not occur without disturbance of the appreciation of position, double contacts, and vibration.

It is impossible, however, to regard it as definitely proved that the loss of recognition of form is co-extensive with loss of these other forms of sensibility, for several patients showed that a very high degree of loss to these latter was compatible with slight loss only in the recognition of form. All we can infer, therefore, is that the appreciation of form is closely associated with the integrity of those paths in the cord that carry the impulses which subserve the sense of position, recognition of two points, and appreciation of vibration.

Shape.—Like the recognition of form, that of shape in two dimensions could be tested on the upper extremities only, but the frequency of its affection seemed much greater than that of form. It is, however, a much more difficult test even for the normal individual with his eyes shut to tell the shape of an object when it is pressed on his palm than it is to recognize its form when he is allowed to handle it, and the controls were not invariably correct in the tests for shape as they were in those for form. A considerable number of mistakes therefore must be regarded as within the limits of experimental error. Making every allowance, however, for the difficulty of the test there appeared altogether too many instances of gross lack of appreciation of shape to neglect this quality of sensibility entirely in estimating the sensory disturbance in Friedreich's disease.

In five patients, at least, there was gross loss; these patients were either unable to recognize the shape of the objects pressed on their hands, or made so many mistakes in attempting to do so that they seemed to have no idea of the shape at all. Most of them when allowed to handle the objects could tell the shape fairly well, except the two patients who had marked loss in the recognition of form, and who were included amongst the five patients with gross defect in the recognition of shape. There was no patient, indeed, with any loss in the recognition of form who did not also show some disturbance in the appreciation of shape, and this latter was usually much the greater.

In some of the patients with pronounced loss of appreciation of shape there was a very slight tactile loss on the hands, but in none of them did it seem sufficient to account for the inability to recognize shape. In others there was no tactile disturbance, and in none of the five patients was there any pressure-touch loss. The loss of appreciation of shape in these patients, therefore, must be regarded as occurring independently of any disturbance of tactile sensibility.

In all of the five patients the disease was considerably advanced and the loss of the sense of position, of the ability to recognize simultaneous contacts and to appreciate vibration was pronounced or even gross in character in them all.

Size.—In testing the patient's ability to recognize size, round discs varying in diameter from 0·5 to 4 cm. were used, and were pressed firmly and evenly on his palm, the difference in diameter between any two successive discs being 0·5 cm. Usually it was found that the controls could distinguish quite easily any two discs with this difference. Greater differences were always recognized correctly.

In the majority of the patients no definite loss in the recognition of size was demonstrable. Seven patients, however, made many errors in attempting to distinguish discs of 0·5 cm. and 1 cm. difference, and even in some instances discs with a difference of 2 cm.

These were chiefly the patients who were unable to recognize shape correctly, and in some of them there was also very slight loss to cotton-wool touches over the hands. This seemed, however, hardly enough to interfere to any extent with the test, for pressure-touch was quite preserved, and other patients who had just as much tactile loss as these seemed to show no loss in the recognition of size. In all these seven patients the disturbance of the sense of position, the recognition of compass-points and the appreciation of vibration was marked, or gross.

It would seem, therefore, that a certain loss in the recognition of differences in size may be found over the palm of the hands in advanced stages of Friedreich's disease and that it occurs only in patients in whom sense of position, discrimination of compass-points and recognition of vibration are much affected, though not always in proportion to the loss of these elements of sensibility.

Weight.—The recognition of weight, like that of size, is a measurable form of sensibility, and the controls used gave very uniform results. As many as ten of the patients with Friedreich's disease were considered to show definite loss in the appreciation of differences of weight; in four of these, there was slight loss only, but six had considerable or even marked loss.

These six were the same patients that showed gross loss in the appreciation of shape, and defective recognition of size, and they included amongst them the two patients who had considerable loss in the recognition of form. They were all, therefore, in more or less advanced stages of the disease and showed in the upper extremities much loss in the recognition of position, dual contacts and vibration. In comparison with the intensity of this loss indeed, the defect in the recognition of differences of weight could not be described as very great. It seemed, however, to be associated definitely with a gross defect in the recognition of all these other forms of sensibility, for in a few cases in which these were markedly affected, but in which one or other of them seemed spared more than the others, weight loss to any extent was not found. It could not, however, be definitely associated with any one of these elements in particular.

A disturbance of the recognition of differences of weight, therefore, would seem to be found in those patients with Friedreich's disease who have a gross loss of the appreciation of position, simultaneous contacts and vibration, and would seem, moreover, closely associated with a defect in the recognition of size and of shape, and like these two forms of sensibility would seem to occur more frequently than a loss in the recognition of form.

In examining the appreciation of form, shape, size and weight in the hands, it was noticed occasionally that there were slight differences between the two sides similar to that described for the other forms of sensibility.

We are now in a position to review the results of this analysis of the sensory disturbances found in the twenty typical cases of Friedreich's disease, in all stages that we have examined.

The appreciation of touch, pain and temperature are very irregularly affected in the upper extremities, never more than very slightly and often not at all. When loss occurs it is almost always a slight distal blunting to touch, and very rarely to pin-prick, or to heat and cold as well. In the lower extremities these cutaneous elements are more frequently involved, and there is often some distal hypoæsthesia to light touch, or even to pressure-touch, and in many cases also to pin-prick and to heat and cold. It is the other elements of sensation however, chiefly those that are commonly included in the term "deep sensibility," but also the appreciation of simultaneous contacts, and of size, shape and form, that are most severely affected. The sense of position and the recognition of passive movement, the appreciation of double contacts and of vibration are almost always more or less affected, especially in the distal parts of the lower limbs, and not infrequently, though to a less degree, in the upper limbs as well. The frequency and the constancy with which these three elements of sensation are disturbed are indeed characteristic of the disease.

The recognition of shape and form, and the appreciation of size and weight are also affected, but much less frequently and less seriously than the sense of position, the appreciation of compass-points, or of vibration. This is probably due to the fact that these forms of sensibility can be examined in the upper extremities only where the sensory loss as a whole in the early stages of the disease is usually not great, and possibly also to the fact that they are more elaborate forms of sensibility. They would seem, however, to be associated in their disturbance rather with the loss of the sense of position, the appreciation of double contacts and of vibration than with tactile loss. The recognition of shape, and that of size and of weight are affected with the same frequency, and usually in the same patients, while the recognition of form is less often disturbed.

The elements of sensibility, therefore, which it is assumed are conducted through the dorsal columns of the cord, would seem to be disturbed in Friedreich's disease more or less constantly and characteristically. The loss, especially in the early stages of the disease, falls most heavily on the lower extremities, that is on the regions innervated by the spinal segments that are earliest affected, and tends to spread higher and higher over the body and to become more profound as the disease advances.

Those elements of sensibility that are conducted through the dorsal columns have been divided into two groups. The recognition of two points of the compasses, and the appreciation of size, shape and form which are dependent at the periphery on the integrity of the cutaneous nerve-endings would seem to run in one group; and the sense of position and of movement, the recognition of vibration and the appreciation of weight, which are dependent peripherally on nerve-endings in joints, tendons, and muscles, apparently compose another group. As the disturbance of the sense of position, of double contacts and of vibration was always so great in every case in which the recognition of size, shape, form, and weight was affected, it is impossible to correlate the disturbance in recognition of size, shape and form with that in the recognition of compass-points particularly; or the loss in appreciation of weight with that of position. In the description of the fate of these elements of peripheral sensibility, therefore, I have preferred for convenience to follow the order in which they were tested clinically, and to consider together the disturbance of the sense of position and of movement, the loss of appreciation of double contacts and the diminished recognition of vibration which constitute a more primary group; the recognition of form, shape, size and weight, would seem to compose a group of more secondary and elaborate sensations.

In a disease such as Friedreich's ataxy where there is a very slow progressive degeneration of the dorsal columns of the cord it is inevitable that though the sensory loss may conform to a definite type there must be much variability in the relative intensity of the affection of the different elements of sensibility in different cases. The frequency, however, with which a characteristic sensory loss does occur would seem to justify its inclusion in the clinical picture of the disease as an integral, not as an exceptional, feature; and further, the constancy and regularity with which this loss involves the sensory impulses assigned to the dorsal columns of the cord goes to confirm the conclusions regarding sensory conduction in the cord that have been obtained by the clinical and anatomical study of local spinal lesions.

BIBLIOGRAPHY.

[1] Bing. "Vibrationsgefühl," *Neurol. Centralbl.*, 1900, Bd. xxix, S. 173.

[2] *Idem.* "Die Abnützung des Rückenmarks (Friedreichsche Krankheit und Verwandtes)," *Deutsche Zeitschr. f. Nervenheilk.*, 1904, Bd. xxvi, S. 163.

[3] Biro. "Einige Mitteilungen über die Friedreichsche Krankheit," *Deutsche Zeitschr. f. Nervenheilk.*, 1901, Bd. xix, S. 164.

[4] Bonnus. "Maladie de Friedreich à début tardif," *Bull. de la Soc. Anat. de Paris*, 1897, 5me sér., t. xi, p. 18.

[5] Bramwell. "Notes on Three Cases of Friedreich's Ataxia," *Brit. Med. Journ.*, 1897, vol. ii, p. 896.

[6] Dejerine. "Sur une forme particulière de maladie de Friedreich avec atrophie musculaire et troubles de la sensibilité," *La Méd. moderne*, 1890, t. i, p. 477.

[7] *Idem.* "Sur les causes probables de l'intégrité de la sensibilité dans la maladie de Friedreich," *Compt.-rend. de la Soc. de Biol.*, 1890, 9me sér., t. ii, p. 105.

[8] *Idem.* "Du rôle joué par les lésions des racines postérieures dans la sclérose médullaire des ataxiques," *Sem. méd.*, Paris, 1892, xii, p. 501.

[9] Dejerine et André-Thomas. "Les lésions des racines, des ganglions rachidiens et des nerfs dans un cas de maladie de Friedreich," *Rev. neurol.*, 1907, t. xv, p. 41.

[10] Dejerine et Letulle. "Etude sur la maladie de Friedreich. Sclérose névroglique pure des cordons postérieurs," *Compt.-rend. de la Soc. de Biol.*, 1890, 9me sér., t. ii, p. 127.

[11] Egger. "La sensibilité osseuse," *Rev. neurol.*, 1908, t. xvi, p. 345.

[12] *Idem.* "La Baresthésie," *Rev. neurol.*, 1907, t. xv, p. 584.

[13] *Idem.* "L'épuisement rapide de la sensibilité au contact et à la pression," *Rev. neurol.*, 1907, t. xv, p. 294.

[14] Greenless and Purvis. "Friedreich's Paralysis," *Brain*, 1901, vol. xxiv, p. 135.

[15] Head, Rivers and Sherren. "The Afferent Nervous System from a New Aspect," *Brain*, 1905, vol. xxviii, p. 99.

[16] Head and Thompson. "The Grouping of Afferent Impulses within the Spinal Cord," *Brain*, 1906, vol. xxix, p. 537.

[17] Head and Holmes. "Sensory Disturbances from Cerebral Lesions," *Brain*, 1911-12, vol. xxxiv, p. 102.

[18] Jumentié et Chenet. "Troubles de la sensibilité dans un cas de maladie de Friedreich," *Rev. neurol.*, 1909, t. xvii, p. 944.

[19] Ladame. "Friedreich's Disease," *Brain*, 1890, vol. xiii, p. 467.

[20] Lambrior. "Un nouveau cas de maladie Friedreich avec autopsie," *Rev. neurol.*, 1913, t. xxv, p. 57.

[21] Mackay. "Pathology of a Case of Friedreich's Disease," *Brain*, 1898, vol. xxi, p. 435.

[22] Marbé. "La sensibilité stéreognostique et la symbolie aux membres inférieurs," *Rev. neurol.*, 1908, t. xvi, p. 351.

[23] MAY, PAGE. "The Afferent Path," *Brain*, 1906, vol. xxix, p. 742.

[24] MINGAZZINI. "Weitere Beiträge zum Studium der Friedreichschen Krankheit," *Arch. f. Psychiat.*, 1897, Bd. xlii, S. 917.

[25] MÜLLER. "Zur Pathologie der Friedreichschen Krankheit," *Deutsche Zeitschr. f. Nervenheilk.*, 1907, Bd. xxxii, S. 137.

[26] NEUTRA. "Ueber Ermüdungsphänomene auf dem Gebiete der Vibrationsempfindung," *Neurol. Centralbl.*, 1904, Bd. xxiii, S. 510.

[27] NOÏCA. "Trouble de la sensibilité objective dans la maladie de Friedreich," *Rev. neurol.*, 1908, t. xvi, p. 92.

[28] ORMEROD. "A Case resembling Friedreich's Disease with Unusual Sensory Loss," *Brain*, 1905, vol. xxviii, p. 92.

[29] *Idem.* "Friedreich's Disease," *Med. Chir. Trans.*, 1885, vol. lxviii, p. 147.

[30] *Idem.* "On the Morbid Anatomy of Friedreich's Disease," *Brain*, 1889, vol. xi, p. 406.

[31] PETRÉN. "Ein Beitrag zur Frage vom Verlaufe der Bahnen der Hautsinne im Rückenmarke," *Skandinav. Arch. f. Physiol.*, 1902, Bd. xiii, S. 9.

[32] *Idem.* "Ueber die Bahnen der Sensibilität im Rückenmarke," *Arch. f. Psychiat.*, 1910, Bd. xlvii, S. 495.

[33] RENNIE. "Friedreich's Ataxy with Necropsy," *Brit. Med. Journ.*, 1899, vol. ii, p. 129.

[34] ROTHMANN. "Ueber die Leitung der Sensibilität im Rückenmarke," *Berl. klin. Wochenschr.*, 1906, Bd. xliii, S. 47.

[35] SEIFFER. "Ueber die Friedreichsche Krankheit und ihre Trennung in eine spinale und cerebellare Form," *Charité Annalen*, 1903, t. xxvi, p. 413.

[36] SOTTAS. "Contribution à l'étude des dégénérescences de la moelle consécutives aux lésions des racines postérieures," *Rev. de Méd.*, 1893, t. xiii, p. 290,

[37] THOMPSON. "A Case of Subacute Combined Degeneration of the Spinal Cord demonstrating the Nature of the Afferent Impulses in the Posterior Columns," *Brain*, 1911-12, vol. xxxiv, p. 510.

[38] WHYTE. "Four cases of Friedreich's Ataxia," *Brain*, 1898, vol. xxi, p. 72.

THE WASSERMANN REACTION AND ITS APPLICATION TO NEUROLOGY.

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THE intention of this paper is to review the present state of knowledge of the Wassermann reaction in all particulars which bear directly or indirectly upon neurology, but in these particulars only. It is also the intention to describe fully the methods which we have ourselves utilized as being the most satisfactory according to our deductions. These deductions are based upon researches into the subject of syphilis generally, and also upon the results of a long collaboration with Dr. Henry Head and Dr. Fearnsides upon syphilis of the nervous system in particular.

The work is treated largely from the technical point of view, and thus assumes a general knowledge of the principles, and even of the technique, of the reaction on the part of the reader. We have not discussed the theory of the subject, since that has no application to neurology, neither have we reviewed the modified tests.

The paper is intended to be read in conjunction with works published or forthcoming by Dr. Head and Dr. Fearnsides and ourselves, and references to cases are constantly made by means of index numbers, which remain the same throughout all these papers.

We desire to record our indebtedness to Professor Bulloch, whose influence, we hope, may be detected throughout.

CHAPTER I.—THE TECHNIQUE OF THE WASSERMANN REACTION.

INTRODUCTION.

Since the inception of the idea of the Wassermann reaction numerous modifications have been suggested with a view to simplification and improvement. The simplified methods have usually led to the introduction of relatively fundamental alterations, and have only enjoyed a vogue when the original method has been inconvenient or looked upon as tedious. On the other hand, notable improvements in detail upon the original description have been suggested, and adopted more or less universally after laborious justification. A reduction in the absolute quantity of the reagents is now general. Watery antigens have been replaced almost entirely by alcoholic or other extracts, and the original severity of the controls for the antigen and other reagents has long been lightened. These improvements do not, of course, enjoy universal recognition, and therefore it is found that the technique adopted by one observer commonly differs from that of another, and in this manner a certain diversity of result is inevitable. It has been suggested that a Commission should inquire into and adjudicate upon the most suitable technique to adopt, but unfortunately there is no finality in medicine, and the selected method would soon be surpassed, if, indeed, it was ever accepted.

As the result of the variety in the technique, the mere statement that a particular "Wassermann reaction" is negative is insufficient; before the value of such an observation can be appreciated, it is essential to know the methods by which it has been arrived at, and the general results which these methods usually yield. We, therefore, describe our technique in full.

REAGENTS.

The reagents required in the performance of the Wassermann reaction are as follows:—

(1) Antigen.
(2) Serum or cerebrospinal fluid to be tested.
(3) Complement.
(4) Hæmolytic amboceptor.
(5) Blood Corpuscles.
(6) Saline solution.

Antigen.

Ever since the earliest days of the Wassermann reaction, discussion has centred round the antigen, not only from the point of view of obtaining the most efficient preparation, but also of inquiring into the ultimate nature of the reaction.

The belief that the interaction of the antigen and syphilitic serum represented a true antigen-antibody combination was early shaken by the demonstration by Marie and Levaditi [30] that an extract of a normal liver could replace an extract of a syphilitic liver in the reaction. This discovery was again followed by the independent observations of Landsteiner, Müller and Pötzl [20], Porges and Meier [46], and Levaditi and Yamanouchi [22], which showed that the Wassermann "antigen" differed from most true antigens in being soluble in alcohol, and was presumably of the nature of a lipoid.

From this time dated the attempts to replace the complicated organ-extracts with pure solutions of lipoids. Porges and Meier were the first to use alcoholic solutions of lecithin with advantage. Levaditi and Yamanouchi found sodium taurocholate and glycocholate to be possessed of antigenic value, and to a less extent lecithin. These last observers found cholesterin to be without effect. Hans Sachs [50] then, in conjunction with Altmann, entered the experimental field with sodium oleate, and later, with Rondoni [52], introduced the artificial mixture of lecithin, sodium oleate, oleic acid, and alcohol. This mixture was tested by Facchini [13], and Eisenberg and Nitsch [12], and found to give satisfactory results.

Noguchi [36] has endeavoured to isolate the reacting substance from alcoholic extracts of animal organs by a process of fractional solution and precipitation. In this way he separated the non-specific inhibiting and hæmolytic substances from the antigenic constituents. These latter, consisting mostly of lecithin, were to be found in the acetone-insoluble fraction. This work was continued with the assistance of Bronfenbrenner [37].

A notable advance was then made by Browning, Cruickshank and Mackenzie [7 and 8], who found that, though cholesterin alone had no antigenic effect, mixtures of lecithin and cholesterin gave a particularly specific reaction with syphilitic serum.

These authors have laid it down that if the addition of cholesterin is capable of increasing the quantity of complement absorbed beyond the amount absorbed by lecithin alone, this is an indication of the syphilitic nature of the serum used.

While the study of isolated constituents of the antigen was thus proceeding, attention was also directed to crude extracts of various animal tissues. The alcoholic extract of syphilitic liver was of course widely used, but, owing to the variation in the quality of different samples, fell into disfavour in many quarters. Landsteiner, Müller and Pötzl introduced alcoholic extracts of guinea-pig heart, and Michaelis [32] human heart. This last was thoroughly tested by Thomsen [55] and Boas, and is used as a routine in the Statens Seruminstitut at Copenhagen. A slight modification by Lesser [21] utilized a watery emulsion of the residue obtained by evaporating an ether-extract of human heart. This antigen has been found by Dembowski [10] to be better than a simple alcoholic extract of heart or an extract of syphilitic liver.

Acetone extracts of dried organs have been suggested by Kolle and Stiner [19].

The latest notable advance in the preparation of antigens has been the suggestion of Hans Sachs [49] to combine the alcoholic extracts of animal organs with cholesterin, thus utilizing the increased effect of this substance demonstrated by Browning, Cruickshank and Mackenzie. The addition of cholesterin to extracts of organs was found by Sachs to endow these, however unsatisfactory alone, with properties equal to those possessed by the best syphilitic extracts. The mixtures had the further advantage of being cheap and obtainable in unlimited amount.

In order to determine the antigen most suitable to our methods we undertook a series of comparative tests upon the same sera, using different antigens [28].

We selected for comparison the following representative forms :—

(1) Alcoholic extract of syphilitic liver (Wassermann).

(2) Alcoholic extract of human heart (Michaelis).

(3) Alcoholic solution of lecithin and cholesterin (Browning, Cruickshank and Mackenzie).

(4) Alcoholic extract of animal organs with cholesterin (Sachs).

Having tested these antigens upon over 500 sera and cerebrospinal fluids we arrived at the conclusion that an antigen prepared from human heart and cholesterin showed a notable improvement upon the others, in that a much higher percentage of positive results was obtained in undoubted syphilis, while no tendency towards non-specificity was observed.

We found that in cases of manifest syphilis, primary, secondary, and tertiary combined (84 sera), the heart-cholesterin antigen gave 14 per cent. more positive results than a good syphilitic liver-antigen; 16 per cent. more than heart-antigen, and 17 per cent. more than lecithin-cholesterin antigen.

In the case of latent syphilis, that is, in syphilitic patients without symptoms and those under treatment, the improvement was still more obvious.

The advantage of this antigen was further particularly apparent in syphilis of the central nervous system including "parasyphilis." Fifteen in fifty-six of these sera gave positive results with heart-cholesterin when heart extract alone was negative. Similarly six sera in thirty-one were positive with heart-cholesterin when syphilitic liver gave a negative reaction. The poorest results were obtained with lecithin-cholesterin. When testing cerebrospinal fluid, however, the lecithin-cholesterin antigen gave slightly better results than syphilitic liver or heart, but not so good as heart-cholesterin, six being negative out of twenty-one, when heart-cholesterin was positive.

It must be clearly understood that these figures only denote the results obtained on the actual samples tested, and have no bearing upon the relative results which might be obtained with the different antigens in other collections of cases. It may be stated that the most obvious differences were encountered in cases of "cerebral syphilis," and so much was this the case that we were compelled to discard a number of tests which had been carried out with heart-antigen for this present investigation and to start *de novo*. Whenever the Wassermann reaction is referred to in this series of papers, the use of heart-cholesterin antigen is implied.

Another highly important advantage of the heart-cholesterin antigen lies in its invariability as demonstrated by us [28]. It has been held very generally, especially in Germany, that a complete quantitative titration of a serum in the reaction is of little value owing to the great error introduced, especially by the variation in antigens. We have, however, always applied this procedure, and particularly after the works of Thomsen and Boas demonstrated its exactitude when using heart-antigen. In practice, however, it was evident that some samples of heart-antigen varied, but this variation appeared to be almost entirely eliminated by the addition of cholesterin. Thus we have always found that a quantitative estimation may be carried out with entirely different reagents and antigens at different times with a very small margin of error (*vide* p. 209).

Example showing a quantitative Test of one Syphilitic Serum, using twenty-four different heart-cholesterin antigens. Result of twelve Antigens only shown, the others were similar.

Syphilitic serum	Antigen No.											
	13	14	15	16	17	18	19	20	21	22	23	24
c.c.												
0·075	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++
0·052	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++
0·042	+++⊥	+++⊥	+++⊥	+++	+++	+++⊥	+++⊥	+++⊥	+++	+++	+++	+++
0·031	++	+++	+++	++	+++	+++	+++	+++	++	+++	++	++
0·023	+	++	++	+	+	+	+	+	+	+	+	+
0·017	0	+	+	0	0	0	0	0	0	0	0	0

(The + signs are proportional to the degree of *inhibition* of hæmolysis. Thus ++++ = No hæmolysis in the sense of a complete positive Wassermann reaction. +++⊥ = trace of hæmolysis.)

Since various samples of heart-cholesterin antigen of equal value can readily be prepared, it follows that this factor at least presents no difficulty in a quantitative estimation.

The heart-cholesterin antigen is prepared in the following way :—

Obtain a fresh human heart and remove from it the muscular portions of the left ventricle free from fat. It is immaterial whether the heart is diseased or not. The muscle is then passed through a mincing machine and 10 grm. of the mince are ground up with 90 c.c. of absolute alcohol for a short time with clean sand. The whole is then transferred to a stoppered bottle and shaken for one and a half hours in a "shaker" at room temperature. Finally, filter through paper and preserve in the ice-chest. The heart extract should be kept for several days before it is first used and filtered again if a precipitate forms in the cold. In a well-stoppered bottle this antigen should keep in the ice-chest for six months. A 1 per cent. solution of cholesterin (Kahlbaum) in absolute alcohol is also made up. It will be necessary to apply heat and thorough shaking to obtain complete solution. For use in the reaction three parts of the heart-extract are mixed with two parts of the cholesterin solution.

As shown long ago by Sachs and Rondoni [53], the method of dilution of antigens is important in order to obtain the best results in each case. Generally they should be mixed with the saline *slowly*. The improved effect is not present with every serum tested but in some cases it is very marked. With our heart-cholesterin antigen, however, the method of mixing does not appear to have much effect upon the antigenic properties, though it is usually found that *rapid* mixing is most efficacious. Thus this antigen should always be placed in a large test-tube and the requisite quantity of saline added *suddenly*.

A heart-cholesterin antigen approximating to our formula has been used by Walker and Swift [58]. These authors have confirmed our statements as to its properties in every particular, and they arrived at the same conclusions by independent lines of investigation. In addition they have elicited the fact that guinea-pig's heart is of equal value to human heart in the preparation of the mixture, and thus have introduced a modification which under certain circumstances may be convenient. The results of Walker and Swift confirm our belief that an antigen such as we have described is an essential for the successful carrying out of the reaction.

Serum and Cerebrospinal Fluid.

The blood to furnish the test serum was always withdrawn from the patient's thumb according to the well-known technique elaborated by A. E. Wright.[1]

This method of bleeding is much quicker than venepuncture when a sufficient skill has been acquired by practice. Suitable apparatus is essential, and so far as we are aware cannot be purchased upon the market.

The capsules are made in the usual manner from best glass tubing, about 7 mm. external diameter. The barrel of the capsule should measure 3 in. (7·5 cm.) and will thus have a capacity of about 1·5 c.c. The curved entering end should have as wide a bore as possible. A right-angled bend is then constructed on the entering end and the glass cut off, as shown in the diagram (fig. 1). The straight end of the capsule is drawn out to a short point to facilitate sealing after use.

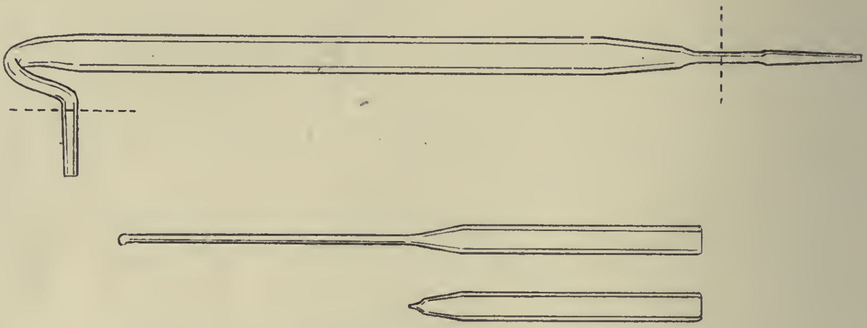

FIG. 1.—Showing the construction of a capsule and "pricker."

The "prickers" are made from narrower glass tubing about 5 mm. external diameter. The glass is first drawn out to make two pipettes and then the capillary part of the tube near the shoulder is again drawn out in the Bunsen bye-pass. The point thus made is broken off short as in the diagram (fig. 1).

Proceed as follows: The right hand of the patient is smartly shaken downwards, either by the patient himself or by the operator, in order to drive the blood into the finger-tips. If the hand is previously cold it should be warmed in hot water. Then without delay a piece of rubber tubing [5 mm. diameter and 18 in. (about 45 cm.) long] is wound round the right thumb from the base to the joint. The first turn of the tubing is locked by the second (*see* fig. 2), and the last is secured by the operator's left index-finger placed on the pulp of the patient's thumb, the operator's thumb being placed against the patient's knuckle, thus compressing the distal phalanx of the thumb.

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[1] For general principles and methods see Sir A. E. Wright, "Technique of the teat and capillary glass tube." London, 1912. Constable.

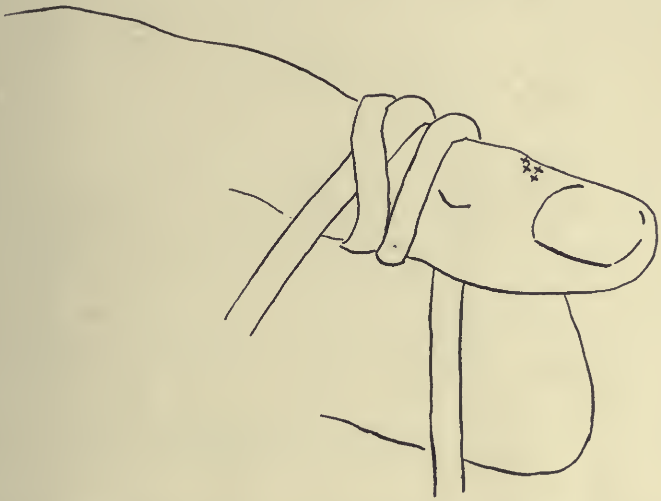

FIG. 2.—Showing the tourniquet in position and the site of the punctures.

Four rapid stabs are then made at the point indicated by crosses, this point being held uppermost. The blood which issues may be collected at the site of the punctures or may be allowed to collect in a pool at the base of the patient's nail. The curved end of the capsule is then applied to the blood in such a way that the body is at the lowest point (fig. 3). The blood will then run in by gravity, being assisted by a "scooping" motion of the capsule. When no more can be expressed the remnant of blood is wiped away, the tourniquet removed and the whole process repeated until the capsule is two-thirds full. It is, however, unnecessary to puncture the thumb a second time. During the operation the capsule may be placed on the table with the short bend at the entering end pointing upwards.

In the case of a "full-blooded" individual the requisite quantity of blood may be collected at one application of the tourniquet, but others may require four or five. When the capsule is two-thirds full the straight end is sealed in a flame and, after clotting has taken place, the blood is shaken down into the closed end.

The clot is separated from the serum in the centrifuge, but before centrifuging the curved end is cut off, as otherwise the capsule is apt to break. The tube is also numbered with grease pencil. After centrifuging for a minute or two, the tubes are supported on end in "plasticine" and the serum is pipetted off and inactivated at 55° C. for thirty minutes in the water-bath. The pipettes may be carried in a float as shown in the figure (fig 4). It is desirable to inactivate the serum within twenty-four hours after bleeding, and in this condition it will retain its properties for a long time.

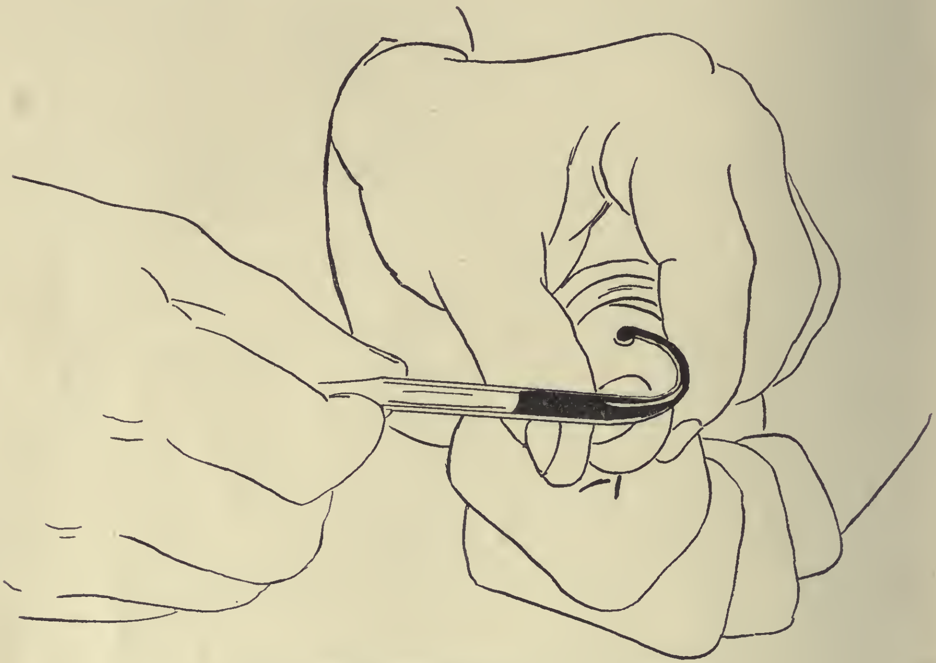

Fig. 3.—Showing the general position for bleeding.

The effect of heat upon the test fluids.—In the case of serum there is no difference of opinion as to inactivation. It is always heated. With the cerebrospinal fluid, however, the practice of different observers varies.

We have always used this fluid *unheated.*

So far as concerns the neurological literature dealing with the Wassermann reaction, we have been unable to find much reference to the effect of heat upon the reacting substance. It will be remembered that originally upon the introduction of the reaction, it was stated that the test-serum must be "inactivated" in order to destroy any

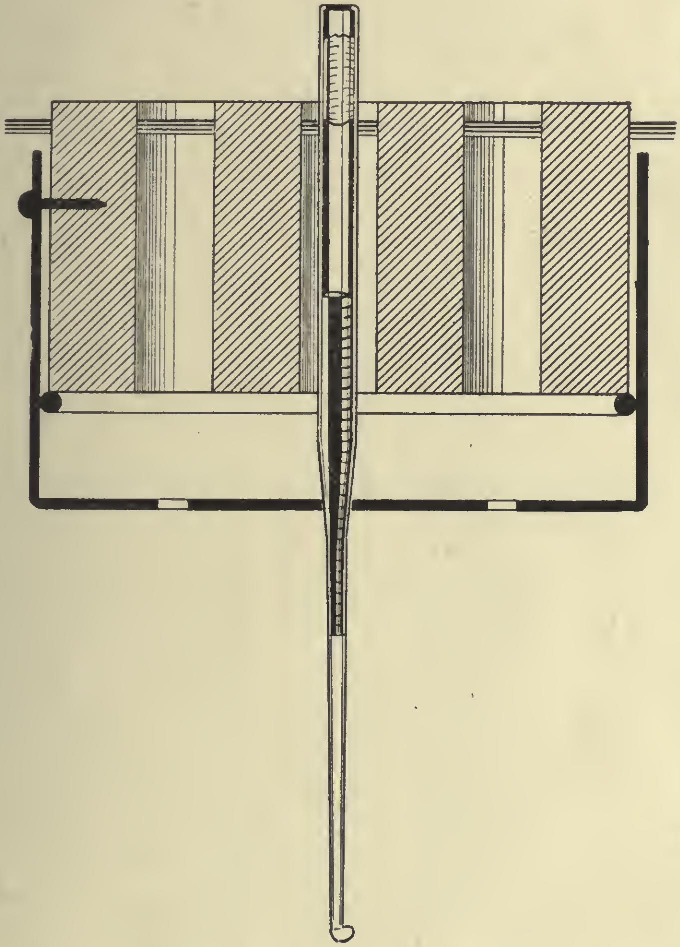

FIG. 4.—Section of the "float" used for supporting the pipettes in the water-bath. A circular copper box is fitted with a large cork stopper (oblique shading). This stopper is held in position by a pin at the side, and rests upon a shelf of copper wire. It is pierced with eight circumferential holes and one central; these correspond in position with nine smaller holes in the bottom of the copper box. The size of both sets of holes is so adjusted that a pipette will readily pass through the cork and rest with its shoulder upon the copper. The contrivance, when fully loaded, will float with its upper surface on the water level.

normal complement, which would interfere with the Bordet-Gengou phenomenon. It was, however, soon shown by Sachs and Altmann [51] that such inactivation was most necessary because a non-syphilitic "active" serum might give a positive Wassermann reaction. Numerous instances of such were given by Boas [4] and by ourselves. If inactivation was omitted a syphilitic serum might give a negative result by reason of excess of complement, while a non-syphilitic serum might give a positive owing to the presence of a non-specific thermolabile body [24].

The nature of the body in a normal active serum which gives a positive Wassermann reaction has not been studied in much detail, and is usually looked upon as similar to the true Wassermann substance. Noguchi [35] was among the first to study the effect of heat upon the serum and demonstrated that a temperature of 55° C. produced a very marked destruction of the "syphilis antibody," to such an extent that at the end of thirty minutes 25 per cent. only of the previous content was available. The most rapid destruction took place in the first five minutes. Noguchi appeared to look upon the bodies destroyed as true Wassermann substances, although he admitted that a normal active serum contained non-specific bodies which were capable of giving "Wassermann reactions" with certain fractions of an alcoholic antigen. He therefore introduced his special antigen which was designed for use with active serum, in order to avoid loss by heat; this antigen did not react with the non-specific body in the serum.

Thomsen and Boas [56] also looked upon the reacting substance as destructible by heat in variable degrees. They considered that substances might appear in the serum in the course of several diseases, including syphilis, which gave a positive Wassermann reaction. These diseases, however, generally differed from syphilis in that the reacting substance was more easily destroyed by heat in the former than in the latter, and thus in them the reaction would be negative. But, in syphilis also, the reacting substance in primary and latent syphilis was more readily destroyed than in secondary cases; thus these would tend to be negative while the secondary sera were positive.

We have found the effect of heat upon the serum to be as described by Noguchi and have also noted that an "active" serum from a patient with latent syphilis (giving a negative reaction on inactivation), contains more non-specific reacting substance than a normal active serum. Nevertheless, we are not altogether disposed to look upon the non-specific reacting body as similar to the Wassermann body, nor to admit that the Wassermann body is in fact destroyed by heat to such a marked extent as is usually stated.

In order to test the matter more accurately we have utilized the

Wassermann body as found in the cerebrospinal fluid, since in this way the difficulties associated with the complex constituents of serum may be avoided. The cerebrospinal fluid contains none of the non-specific reacting body which is present in an unheated serum.

We have found that in dementia paralytica and tabes dorsalis heat does not materially reduce the strength of the reaction as found in the cerebrospinal fluid.

Experiment showing the Effect of Heat (55° *C.*) *upon the Reaction of the Cerebrospinal Fluid in two Cases of Tabes dorsalis.*

Example 1.

Amount of cerebrospinal fluid	Unheated	Heated in water-bath for Minutes						
		5	10	20	30	40	50	60
0·2 c.c.	++++	++++	++++	++++	++++	++++	++++	++++
0·1 ,, ...	++++	++++	++++	++++	++++	++++	++++	++++
0·05 ,, ...	++++	++++	++++	++++	++++	++++	++++	++++
0·02 ,, ...	+++	+++	++	+++	++	++	0	0
0·01 ,, ...	0	0	0	0	0	0	0	0

(++++ = Positive reaction. 0 = Negative.)

Example 2.

Amount of cerebrospinal fluid	Unheated	Heated in water-bath for Minutes				
		5	10	20	30	40
0·2 c.c.	++++	++++	++++	++++	++++	++++
0·1 ,, ...	++++	++++	++++	++++	++++	++++
0·05 ,, ...	++++	++++	++++	++++	++++	++++
0·02 ,, ...	++	0	0	0	0	0
0·01 ,, ...	0	0	0	0	0	0

(++++ = Positive reaction. 0 = Negative.)

In cerebrospinal syphilis, however, the effect of heat is somewhat more marked, although even in this case it falls far short of the apparent effect observed in the case of serum.

Experiment showing the Effect of Heat (55° *C.*) *upon the Reaction in the Cerebrospinal Fluid in two Cases of Cerebrospinal Syphilis.*

Example 1.

Amount of cerebrospinal fluid	Unheated	Heated in water-bath for Minutes			
		5	10	20	30
0·2 c.c.	++++	++++	++++	++++	+++
0·1 ,, ...	++++	+	0	0	0
0·05 ,, ...	0	0	0	0	0
0·02 ,, ...	0	0	0	0	0
0·01 ,, ...	0	0	0	0	0

(++++ = Positive reaction. 0 = Negative.)

Example 2.

Amount of cerebrospinal fluid	Unheated	Heated in water-bath for Minutes			
		5	10	20	30
0·05 c.c...	++++	++++	++++	++++	++++
0·02 ,, ...	++++	++++	++++	++++	++++
0·012 ,, ...	++++	++++	++++	++++	++++
0·006 ,, ...	++++	++	++	++	+
0·003 ,, ...	0	0	0	0	0

(++++ = Positive reaction. 0 = Negative.)

We, therefore, conclude that inactivation of the cerebrospinal fluid does not lead to any material destruction of the reacting substances except in cerebrospinal syphilis, and even in this case the destruction is slight when compared with that which occurs in the serum. In our view this result is explicable on the assumption that the Wassermann body proper is practically unaffected by heat. In those cases, however, in which the syphilitic process is most active (cerebrospinal syphilis), the cerebrospinal fluid contains additional bodies derived from the blood fluids in the form of an acute exudate, and these bodies not only tend to give a stronger Wassermann reaction, as in the case of "active" serum, but are also more thermolabile.

It will be remembered from the work of Weil and Kafka [59] that in acute infective meningitis the cerebrospinal fluid contains the normal "anti-sheep hæmolysins" of the serum, both amboceptor and complement. In dementia paralytica, on the other hand, no complement was present and the amboceptor in less amount only. These authors suggested this phenomenon as a means of differential diagnosis between dementia paralytica and acute meningitis. They did not, however, test the cerebrospinal fluid from the acuter cases of syphilitic meningitis. In our view their work suggests that in the acuter cases, whether syphilitic or not, the constituents of the cerebrospinal fluid tend to approximate more nearly to those of the serum than in the chronic cases (dementia paralytica and tabes dorsalis, &c.). The non-specific body of the serum will therefore be found in the cerebrospinal fluid in the acute syphilitic lesions more often than in the chronic. Thus the use of unheated cerebrospinal fluid in the cerebrospinal cases in particular will determine a stronger reaction than heated fluid, and, no doubt, this stronger reaction will be to some extent "non-specific" as in the case of unheated serum, but in practice this "non-specificity" is negligible. An unheated cerebrospinal fluid does not give a positive

Wassermann reaction except in a case of syphilis of the central nervous system, and, therefore, inactivation of this fluid should not be carried out.

We have no doubt that neglect of this precaution has occasioned some of the poor results recorded by those who follow the "original" technique.

It is not possible, however, to determine exactly to what extent this disturbing factor is present owing to the absence of technical data in many published papers, and to the use of loose expressions as to the "original method" in use. The "original method," as now described by the great authority Plaut [43], requires the use of an aqueous extract of syphilitic liver and inactivation of the cerebrospinal fluid. G. Meier [31], on the other hand, who has also been closely associated with Wassermann, now uses an alcoholic extract of syphilitic liver, while cerebrospinal fluid—"braucht nicht inaktiviert zu werden." Clearly, therefore, the use of the expression "original method" conveys a different meaning in the writings of different observers.

The use of unheated cerebrospinal fluid increases the reacting power of this substance in many cases, but at the same time it puts an end to any exact comparison between the strength of the reaction in the heated serum and the unheated cerebrospinal fluid. This factor must not be lost sight of throughout this paper, as, also, the fact that twice as much cerebrospinal fluid as serum is always used.

The quantity of test fluids.—In addition to the question of heat, much variety in practice is found relating to the *quantity* of cerebrospinal fluid used in the test. Most observers use the same amount of serum in proportion to the other constituents. In the original reaction 0·2 c.c. of cerebrospinal fluid was used in a total volume of 3 c.c. in the fixation stage. It was soon found, however, that more fluid could be used without endangering the result; thus Boas and Lind [6] used 0·4 c.c. in a volume of 3 c.c., and we have always used a maximum of 0·2 c.c. in a volume of 1 c.c. Latterly much attention has been directed in neurological circles to the quantitative method ("Auswertungsmethode") of Hauptmann and Hössli [17], the chief object of which is to use still larger quantities. These observers use a maximum of 1·0 c.c. of cerebrospinal fluid in 3 c.c. instead of 0·2 c.c., that is to say, rather less than twice as much as we have used. This five-fold increase in the quantity of fluid gave greatly improved results (*c.f.* also Ritz and Sachs [48]), but it is doubtful whether this increase is of so much value as is claimed for it. It must be pointed out that the results previously obtained by Hauptmann, notably in tabes dorsalis, were very much inferior to the results obtained by many others using the same small quantities of fluid; and thus the improvement observed by Hauptmann will not be observed to such a marked extent by others. The causes of this diversity are not quite clear, and since we are unacquainted with any full account of Hauptmann's technique, the part played, for instance, by diversity of antigens, cannot be estimated. Some objection has been made to the use of these large quantities, that summation of non-specific anticomplementary action ("Eigenhemmung") is likely to occur, but we have never observed the slightest tendency to "Eigenhemmung" when using cerebrospinal fluid in any quantity.

Quantitative estimations.—In every case the sera and cerebrospinal fluids were estimated quantitatively for their content of reacting substance. It has always been our practice to make the quantitative estimate by varying the amount of serum in the presence of constant amounts of antigen and complement [23]. The maximum quantity of serum used was 0·1 c.c., and this quantity was halved four times, producing the following range: 0·1 c.c., 0·05 c.c., 0·025 c.c., 0·012 c.c., and 0·006 c.c. We have described the result according to the amount which produced complete inhibition of hæmolysis. If complete inhibition may be represented as ++++ in the sense of a complete positive Wassermann reaction, and +++, ++, + stages of inhibition less than complete, we may represent the value of a serum as follows:—

$$\begin{array}{c} ++++ \\ ++++ \\ +++ \\ + \\ 0 \end{array}$$

This figure implies that 0·1 c.c. and 0·05 c.c. produced complete inhibition; 0·025 c.c. and 0·012 c.c. partial inhibition; while 0·006 c.c. allowed complete hæmolysis. In order to economize space, however, we next reproduced the figure as follows:—

4 (plus signs)
4 ,,
3 ,,
1 ,,
0 ,,

or still more shortly W. R. = 4.4.3.1.0.

In a similar manner in the case of the cerebrospinal fluid we may find W. R. = 4.4.4.4.0, and since we have nearly always tested the serum and cerebrospinal fluid together we should represent this result thus:— $\text{W. R.} = \frac{4.4.3.1.0.}{4.4.4.4.0.}$. If the serum was tested alone thus, $\text{W. R.} = \frac{4.4.3.1.0.}{-\ -\ -\ -\ -}$, or if the cerebrospinal fluid alone: $\text{W. R.} = \frac{-\ -\ -\ -\ -}{4.4.4.4.0.}$

It is often held, particularly in Germany, that the factors involved in the reaction are so complicated and variable that no accurate estimation can be made of two samples of serum unless they are tested together at the same time. Undoubtedly such a method is best, but when the sample is taken from the same patient at different times, it is not applicable. We have always found that our technique is sufficiently exact for quantitative purposes. When each successive quantity of serum is half the former, as suggested, it is quite easy to obtain satisfactory results. We have tested the same material five times, each time with different reagents, and have obtained the same result.

Experiment.—Cerebrospinal fluid (Case 189) unheated and kept sterile in the ice-chest.

June 25, 1913 ..	4.4.4.0.0.
July 2, ,, ..	4.4.4.0.0.
July 9, ,, ..	4.4.4.0.0.
July 16, ,, ..	4.4.4.1.0.
July 23, ,, ..	4.4.4.0.0.

Complement.

The complement used was the serum of a guinea-pig. The animal is stunned, and then its throat is cut with a razor, the blood caught in a dish and rapidly transferred to a conical vessel, wherein it is whipped. The blood is next centrifuged and the serum removed. It was always used on the same day.

By the method of freezing, guinea-pig serum may apparently be preserved for several days, but this introduces a factor which is not yet entirely worked out. The serum is placed in a glass capsule and then enclosed in a "thermos" flask with freezing mixture (salt and ice).

Hæmolytic Amboceptor.

This was a sheep-rabbit amboceptor having a minimal hæmolytic dose (M.H.D.), ranging from 0·0003 to 0·0005 c.c. as regards 0·5 c.c of a 5 per cent. sheep's corpuscle suspension, in the presence of 0·1 c.c. of complement diluted 1 in 2.

Whatever the technique of preparation employed, the production of a suitable amboceptor is always a matter of chance and therefore several rabbits should be injected at the same time. When sufficient "titre" has been attained, the animal is bled aseptically, the serum collected and preserved in small capsules. Samples are removed from these capsules for use when required. The amboceptor retains its properties for many months.

Blood Corpuscles.

These were obtained from the sheep. Although the method of collection at the slaughter-house does not entail any aseptic precautions, the blood will remain in a satisfactory condition for three to six days according to the efficiency of the ice-chest in use.

On each test day some of the blood is centrifuged, the serum removed and the deposit washed three times with saline in a dilution of about 6 to 1.

Saline Solution.

Pure crystallized sodium chloride and distilled water were used. The strength was 0·9 per cent.

STANDARDIZATION OF THE REAGENTS.

Since the Wassermann reaction is a measure of the power of the complex antigen-serum to fix complement, it is necessary to standardize all the reagents.

We take as our constant the hæmolytic amboceptor, the strength of which, having once been estimated, does not vary appreciably. It has been stated and appears to be generally held that a "unit" of amboceptor is not a constant quantity, since it is dependent upon the amount of complement present during its estimation. This is indeed the case when dealing with ox corpuscles, but with those of the sheep we have been unable to confirm the statement. With these corpuscles the quantity of complement, presuming that excess is present, does not have a great effect upon the size of a "unit" of amboceptor.

Amboceptor.

Dilutions of amboceptor are prepared in saline in quantities ranging from 0·0001 c.c. to 0·0009 c.c. as follows:—

Measure[1] 0·1 c.c. of amboceptor into 9·9 c.c. of saline and shake; of this dilution place 1 c.c. in 9 c.c. of saline. The amboceptor will then be diluted in 1 in 1,000 and 0·1 c.c. of the dilution will contain 0·0001 c.c. of amboceptor. Thus 0·1 c.c. to 0·9 c.c. of the dilution are measured into 9 test-tubes, and, after the volume in each tube has been brought to 0·9 c.c. with saline, 0·1 c.c. of a 1 in 2 dilution of complement is added to each, and, finally, 0·5 c.c. of a 5 per cent. suspension of sheep's corpuscles. The total volume is 1·5 c.c. This mixture is shaken and incubated in the water-bath at 37° C. for twenty minutes. The M.H.D. is then read off and three such doses or three "units" are utilized in the Wassermann test. This standardization should be performed with at least two samples of guinea-pig serum in order to ensure that great excess of complement is present. When once the "titre" is arrived at it is not necessary to re-estimate the strength of the amboceptor for several months.

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[1] Suitable pipettes for all measurements are supplied by Messrs. Baird and Tatlock 14, Cross Street, Hatton Garden, London. They are graduated to the point and the scale is more prolonged than in the case of ordinary measuring pipettes. The same firm supplies the other apparatus mentioned in this paper.

Complement.

The guinea-pig complement is diluted 1 in 24 with saline, and of this dilution the following quantities are arranged in test-tubes: 0·1 c.c., 0·125 c.c., 0·15 c.c., 0·175 c.c., 0·2 c.c., 0·25 c.c., 0·3 c.c., 0·35 c.c., and 0·4 c.c. The volume is then made up to 1 c.c. with saline and finally 0·5 c.c. of the corpuscle suspension, sensitized in bulk with 3 M.H.D. of amboceptor per 0·5 c.c. (*vide* p. 213) is added to every tube. Incubate for twenty minutes in the water-bath and read the M.H.D. This will usually be 0·2 to 0·3 c.c. of the 1 in 24 dilution. Two and a half M.H.D. are utilized in the Wassermann reaction, but it is not desirable to take a M.H.D. less than 0·175 c.c. of the 1 in 24 dilution and any complement which does not fully hæmolyse in the 0·3 c.c. tube should be discarded. The standardization of the complement must be carried out every day with the actual suspension of corpuscles in use.

The dilution of the complement is so arranged that the requisite amount for the Wassermann reaction (2½ M.H.D.) is contained in 0·5 c.c.

On calculation it will be found that if the M.H.D. of the 1 in 24 dilution is 0·175 c.c., 0·2 c.c., 0·25 c.c., or 0·3 c.c., it will be necessary to use in the test 0·5 c.c. of a 1 in 27, 1 in 24, 1 in 19, or 1 in 16 dilution respectively.

Antigen.

As already stated, various samples of heart-cholesterin antigen do not differ in antigenic value, so long as the methods of preparation are identical. In practice, therefore, it is quite unnecessary to standardize various samples. When making the antigen for the first time, however, it will be desirable to control the technique of preparation by standardization. The method adopted is to standardize according to anticomplementary effect in the absence of syphilitic serum. As is well known certain of the constituents of the antigen have an inherent destructive effect upon complement, quite apart from the power of "fixation" in the presence of syphilitic serum. This "anticomplementary" effect is the chief factor which determines the amount of antigen to be used in the test, since too great a quantity would leave too little complement free to participate in the specific reaction. The anticomplementary action of many antigens varies in different samples, and thus the quantity selected for use will vary without regard to the true "antigenic" value of the extract. In the case of our antigen, however, the anticomplementary action of different samples is equal [28], as also is the antigenic, and thus standardization by anticomplementary effect will always furnish a reagent of constant value. We determine the "completely inhibiting dose" of the antigen and then select a certain fraction of this which will give a sufficient margin of safety. We therefore utilize in the reaction one quarter of that quantity which will alone produce complete inhibition of hæmolysis after being incubated for one hour with the complement in the air incubator. It will be found that twice this quantity, that is one half of the "completely inhibiting dose" will just permit of complete hæmolysis. With our own methods of preparation the quantity of antigen to use is 0·5 c.c. of a 1 in 15 dilution in saline solution as shown below.

Experiment showing the Anticomplementary Action of the Heart-cholesterin antigen.

Antigen—3 parts of heart + 2 parts of cholesterin, diluted	Quantity of dilution used	Complement 2½ M.H.D.	Result
1 in 10	0·5 c.c.	0·5 c.c.	0
1 in 8	,,	,,	0
1 in 6	,,	,,	++
1 in 4	,,	,,	++++
1 in 3	,,	,,	++++
1 in 2	,,	,,	0

(++++ = complete inhibition. 0 = complete hæmolysis.)

0·5 c.c. of the 1 in 4 dilution is the smallest amount which gives complete inhibition, therefore 0·5 c.c. of a 1 in 16 dilution should be used. Actually we utilize 0·5 c.c. of a 1 in 15 dilution. The strongest solution (1 in 2) produces hæmolysis, owing to the hæmolytic action of soaps and alcohol. It will be noticed that double the test quantity, i.e., 0·5 c.c. of a 1 in 8 dilution permits of complete hæmolysis.

Serum or Cerebrospinal Fluid.

As already stated, 0·1 c.c. of heated serum is the maximum quantity used, while 50 per cent. dilutions are prepared from it. The method is as follows: 0·1 c.c. is measured into the first tube by the method of Donald [11], using drops. Glass pipettes are calibrated by passing them through particular holes in a wire gauge plate until they are held firmly; they are then cut off flush with the plate and it is found that pipettes made in the same hole will drop the same number of drops per cubic centimetre when the instrument is held in the same position. We use hole No. 53 in the Stubbs wire gauge plate, and find that a pipette made in such a manner will furnish 0·1 c.c. of serum in four drops when held vertically. Thus our quantities of serum are prepared as follows :—

0·1 c.c. = 4 drops
0·05 ,, = 2 ,,
0·02 ,, = 1 ,,
0·012 ,, = 4 ,, of a 1 drop in 8 drops dilution
0·006 ,, = 2 ,, ,, ,, ,, ,,

For measuring cerebrospinal fluid, we use the same pipette, although this introduces a trifling error, owing to the different surface tension of the two fluids :—

0·2 c.c. = 8 drops
0·1 ,, = 4 ,,
0·05 ,, = 2 ,,
0·02 ,, = 1 ,,
0·01 ,, = 4 ,, of a 1 drop in 8 drops dilution

We do not in any case trouble to make the total volumes equal with saline, since the difference in bulk is of no consequence.

PRELIMINARY ARRANGEMENTS FOR THE TEST.

The requisite quantities of the reagents for the day's tests are calculated as follows :—

Assume that 20 sera are to be tested. Each serum will require five antigen tubes and one control without antigen—six tubes in all. The sensitized emulsion of corpuscles is first arranged: 6 × 20 = 120 tubes required = 60 c.c. (0·5 c.c. per tube). This is made up as follows :—

Amboceptor 3 M.H.D. per tube = 0·0009 × 120 = 0·108 c.c.
(M.H.D. = 0·0003 c.c.)
Corpuscle deposit .. .. .. = 3·00 ,,
Saline solution .. .. = 56·90 ,,
60·008 ,,

This will provide a 5 per cent. corpuscle suspension, every 0·5 c.c. of which will contain the correct quantity (3 M.H.D.) of amboceptor per tube. The amboceptor is added first to the saline and then the corpuscles. Shake thoroughly. In practice it is usual to make up a small excess of all reagents.

The next operation is to standardize the complement against this sensitized suspension, and while this is proceeding the antigen dilution is prepared as follows :—

If twenty sera are to be tested, 100 antigen tubes will be required or 50 c.c. of antigen (0·5 c.c. per tube). The mixture of heart-extract and cholesterin is diluted 1 in 15. Therefore $\frac{50}{15} = 3·3$ c.c. of the combined antigen will be required, or 1·98 c.c. of heart + 1·32 c.c. of cholesterin. The dilution is therefore made as follows :—

Heart-extract	1·98 c.c.	Mix	Mix rapidly.
Cholesterin solution	1·32 ,,		
Saline	46·70 ,,		
	50·00 ,,		

The heart-extract and cholesterin are mixed together in a large test-tube and the requisite quantity of saline is poured in rapidly. It is now found that 0·25 c.c. of the 1 in 24 dilution of complement is the minimal hæmolytic dose, and therefore 0·25 × 2·5 = 0·625 c.c. of the 1 in 24 dilution should be used in the test or 0·5 c.c. of a 1 in 19 dilution. Fifty cubic centimetres of this (0·5 c.c. per tube) will be required for the antigen tubes, thus 2·6 c.c. of complement added to 47·4 c.c. of saline should be prepared. The 50 c.c. of diluted antigen is added to the 50 c.c. of diluted complement *just before use* and 1·0 c.c. of the mixture is placed in every tube requiring antigen. Twenty control tubes without antigen also require complement; in this case, however, the complement should be diluted 1 in 38 in order to make up the bulk in the absence of antigen. Twenty tubes require 20 c.c. of 1 in 38 complement, that is 0·52 c.c. of complement + 19·48 c.c. of saline; 1 c.c. of this is added to every control tube.

THE TEST.

Suitable test-tubes measure 4 × $\frac{5}{8}$ in. (10 × 1·6 cm.), and are made of stout glass. They are arranged in metal racks holding twenty-four, in four groups of six. Each row of six belongs to one patient, the first five containing antigen and the sixth being a control. It is desirable that all tubes, both in the front row and also in the back be viewed and read off from one side only, i.e., the front, which should be indicated by a mark. If the left and right hand of the rack is thus kept constant there is less liability to confusion when filling in the reagents.

Having measured in all sera first and then the complement with and without antigen, the racks are shaken and put into the air incubator at 37° C. for one hour.

It has been stated that the fixation of the complement in the first stage of the Wassermann reaction proceeds best at a temperature of 37° C. in the water-bath, while others claim that the temperature of the ice-chest is more satisfactory. We have been unable to detect any improvement by these methods over incubation in air at 37° C.; on the contrary, we have found them somewhat inferior. It will be understood that fluid in an air incubator at 37° C. does not reach this temperature for a long time, and therefore such a method really corresponds to incubation at room temperature for much of the period. Thomsen and Boas [57] have shown that the statements regarding improvement in the ice-chest are based upon experimental errors, and have found that fixation proceeds best in most cases at room temperature and in a few at 37° C. in the water-bath. They therefore suggest three-quarters of an hour fixation at room temperature followed by a quarter of an hour at 37° C. in water. Probably the method used by us produces similar results.

Schema of the Test.

							Controls		
Tube	1	2	3	4	5	6	7	8	9
	c.c.	c.c.	c.c.	c.c.	c.c.	c.c.	c.c.	c.c.	c.c.
Serum	0·1	0·05	0·025	0·012	0·006	0·1	—	—	—
or									
Cerebrospinal fluid ..	0·2	0·1	0·05	0·025	0·012	0·2	—	—	—
Antigen .. 0·5 c.c. Complement 0·5 ,,	1·0	1·0	1·0	1·0	1·0	—	1·0	—	—
Saline .. 0·5 c.c. Complement 0·5 ,,	—	—	—	—	—	1·0	—	1·0	—
Incubate for one hour at 37° C. in air.									
Sensitized corpuscles..	0·5	0·5	0·5	0·5	0·5	0·5	0·5	0·5	1·5

Incubate for twenty minutes at 37° C. in water. Then read the results, or allow to stand for one hour at room temperature, without shaking.

After fixation the sensitized emulsion is added and the tubes are shaken. The racks are then placed in water at 37° C. The water-bath is economical of time, since twenty minutes is about equivalent to sixty minutes in the air incubator. After the lapse of twenty minutes the racks are taken out and the results read off, or, to facilitate the recognition of small degrees of hæmolysis, they are first allowed to stand for one hour for the corpuscles partially to settle down.

No special provision is made for known syphilitic and non-syphilitic controls because such are always present in a large series.

It will be noticed that our "controls" differ from those used in the "original technique."

According to the original account it was necessary to show that twice the test quantity of antigen permitted complete hæmolysis. We use only one dose of antigen as control, nevertheless from long experience we have found that twice our antigen dose will permit of hæmolysis, and since our antigen, unlike syphilitic liver-antigens, is not variable, there is no danger in this procedure. Further, the double antigen control is now given up by most followers of the original method. It is the practice to use a larger quantity of antigen in the test, and this quantity will not permit of hæmolysis in double dose. Thus it is clear that so far as antigen is concerned our technique is "safer."

Further, it is the general practice to control the "Eigenhemmung" of the serum and cerebrospinal fluid by "double dose" controls. As we have already pointed out, however, this is quite unnecessary in the case of the cerebrospinal fluid. It is true that serum shows more "Eigenhemmung" than cerebrospinal fluid, but in practice when dealing with fresh, sterile, and quickly heated serum, "Eigenhemmung" is very seldom seen. We control the phenomenon by observing the velocity of the reaction, that is to say, if we find a case in which the single dose of serum does not rapidly hæmolyse, we look upon the result with suspicion.

Interpretation of the Result.

In the great majority of cases it will be found that either complete hæmolysis has occurred in every tube thus : $\frac{0.0.0.0.0.}{-\ -\ -\ -\ -}$, or in one or more tubes there is a complete inhibition, thus : $\frac{4.1.0.0.0.}{-\ -\ -\ -\ -}$. A few cases will, however, be found in which inhibition is present in the first tube, although it is not complete : $\frac{3.0.0.0.0}{-\ -\ -\ -\ -}$; $\frac{2.0.0.0.0.}{-\ -\ -\ -\ -}$ or $\frac{1.0.0.0.0}{-\ -\ -\ -\ -}$. and the question arises as to whether these cases are to be reported positive or not.

The figure $\frac{3.0.0.0.0.}{-\ -\ -\ -\ -}$ represents from a trace to 25 per cent. of hæmolysis.
$\frac{2.0.0.0.0.}{-\ -\ -\ -\ -}$,, ,, 25 to 50 per cent. ,, ,,
$\frac{1.0.0.0.0.}{-\ -\ -\ -\ -}$,, ,, 50 to 75 per cent. ,, ,,

While it is safer to restrict the term "positive reaction" to complete inhibitions in the first tube $\frac{4.0.0.0.0.}{-\ -\ -\ -\ -}$, nevertheless, in practice, we also include slight degrees of hæmolysis up to 25 per cent. under this heading, $\frac{3.0.0.0.0}{-\ -\ -\ -\ -}$, and have not observed any error in diagnosis by so doing; this may be said to be the general practice with regard to the Wassermann test. When, however, the greater degrees of hæmolysis 2.0.0.0.0. or 1.0.0.0.0. are considered, it is necessary to take into account two different conditions.

Firstly, whether it is known to the tester that the serum has reacted positively in his hands on a former occasion, or whether he is ignorant of the antecedents of the case. In general diagnostic work, when nothing is known about a serum, it would be extremely unwise to pay any attention to results shown as 2.0.0.0.0. or 1.0.0.0.0., since there are several non-syphilitic conditions which may give this amount of inhibition, notably some cases of febrile tuberculosis, or pneumonia. If, however, the serum is known to have been positive on a former occasion, it is of importance to record these slight results, since they then indicate that the syphilitic patient has not yet a completely negative reaction. They will, of course, be observed constantly in all cases of syphilis under treatment at some period, and no patient can be looked upon as "cured" so long as such a result is obtained.

We therefore hold that from the strict serological standpoint 2.0.0.0.0. or 1.0.0.0.0. have no diagnostic significance, but nevertheless, may be important from the point of view of treatment.

CHAPTER II.—THE OCCURRENCE OF THE WASSERMANN REACTION.

INTRODUCTION.

THE diagnostic value of a biological test depends largely upon the frequency with which a positive result may be expected. Some reactions when positive may be decisive, but they may be so seldom positive that a great deal of their practical utility is lost. The value of a test is much increased if it is found to be positive so frequently in undoubted examples of the particular condition that a negative result assumes a certain value.

Thus the diagnostic value of the Wassermann reaction depends to a large extent upon the constancy of its occurrence in syphilis. If it is admitted that a positive result is, within limits, undoubtedly indicative of syphilis, it does not of course follow that a negative result will exclude this disease. Numerous cases of undoubted syphilis are known in which the reaction has been negative for reasons explicable or inexplicable. It therefore is clear that a negative reaction does not exclude syphilis; such a result merely introduces a certain improbability into this diagnosis, and the improbability will be greater or less according to the frequency with which negative reactions are usually obtained in cases of syphilis. A negative reaction in acute secondary syphilis is extremely rare, and therefore a diagnosis of secondary syphilis in spite of this result will be extremely improbable. On the other hand, negative results are not so uncommon in tertiary syphilis and therefore such a diagnosis may be made in the face of a negative reaction with greater probability than in secondary syphilis.

This method of reasoning, however, presumes that the results obtained by different apparently competent persons are of equal value; but a short study of the literature is sufficient to show that this is not the case; thus one investigator may find 60 per cent. of cases of tertiary syphilis positive, while another may find 100 per cent. positive. It is clear, therefore, that the average results obtained by the particular tester must be known before the value of his negative result is fully appreciated.

The reputation of the Wassermann reaction depends upon two factors, firstly, the accuracy of the technique employed, and secondly, the accuracy of the clinical diagnosis on which are calculated the percentage results of the serologist.

It is always found that the poorest results are obtained in general diagnostic work, when the sera are sent for examination by a number of clinicians of varying experience and when the correctness of the diagnosis is not open to investigation. The best results, on the other hand, are obtained when the sera emanate from one source of undoubted excellence and in particular when the diagnosis is revised after further investigation of the case along lines suggested by the serological result.

Owing to the above considerations an examination of the literature does not throw much light upon the question of the occurrence of the reaction. It is usually found that if the technique is fully described there is no reference to the accuracy of the clinical diagnosis, while, if the details of the cases are entered into, the serological details are given in an entirely uncritical manner.

In order to avoid this error as far as possible in the present case, we always append to the serological result a reference to a full clinical study of the patient, and, on the other hand, we have given a full account of the methods by which we have arrived at this result.

The Occurrence in General Diagnostic Work.

As a general index of the results obtained by our particular technique, the following figures may be quoted. They represent the routine tests carried out in cases of general syphilis excluding nervous conditions. In every instance the diagnosis was described as being "clinically certain," and in the great majority this was the personal view of Dr. J. H. Sequeira, dermatologist to the London Hospital.

Antisyphilitic treatment had not been practised to any great extent.

Cases of Active Syphilis described as "clinically certain," tested between January, 1912, *and February,* 1913.

	Total	Positive	Negative	Positive per cent.
Primary syphilis	33	31	2	93
Secondary syphilis	109	108	1	99
Tertiary syphilis	195	190	5	97
Congenital syphilis	35	35	0	100

These results are comparable with those published by Boas, and demonstrate the very high degree of accuracy attained by the Wassermann reaction at the present time. It is clear that a diagnosis of active syphilis in the absence of a positive reaction will require very special support before it can be considered probable. As regards the specificity of the reaction, we have only found one non-syphilitic individual giving a positive result in recent years—a case of acute malaria twenty-four hours after a rigor. Other cases of malaria, leprosy, &c., have given negative reactions. We have had no experience of scarlet fever recently, though formerly we have described fleeting positive results.

The Occurrence in Syphilis of the Central Nervous System.

Under this heading we discuss the incidence of the Wassermann reaction not only in cases of cerebrospinal syphilis but also in the so-called "parasyphilitic" conditions. The classification follows the usually accepted clinical demarcations, but it must be stated at once that such demarcations are not absolute. There are so many instances of transitional forms not only between dementia paralytica and tabes dorsalis, but also between these "parasyphilitic" states and admitted "cerebrospinal syphilis," that too much importance should not be directed to exceptions to any "rules" which may be evolved.

The reports in the literature on the Wassermann reaction in neurological cases are extremely variable, and frequently refer only to asylum patients. Relatively little attention has been directed to the study of nerve lesions as found in general hospitals.

We have classified our results under the following headings:—

(1) Dementia paralytica, including the transitional forms of tabo-paralysis.

(2) Tabes dorsalis, including those cases associated with optic atrophy, amyotrophy, and Erb's degeneration.

(3) Cerebrospinal syphilis, subdivided into two groups:—

- (*a*) Those cases in which there is clinical evidence of a lesion of the spinal cord with or without involvement of the brain.
- (*b*) Those cases in which the brain only appears to be affected.

(1) *Dementia Paralytica, &c.*

According to an examination of the earlier literature (1908-1910) already published by us [25], 98 per cent. of cases of dementia paralytica give a positive reaction in the serum, and 85 per cent. in the cerebrospinal fluid. Although these figures denote a high proportion of cases positive, the results obtained by the best methods at the present time give a considerably higher proportion, especially as regards the cerebrospinal fluid. Thus Plaut [42] describes two negative among 320 sera, practically 100 per cent. positive; while in 276 cerebrospinal fluids nine were negative, or 96 per cent. positive.

Being confined entirely to hospital cases, our results in this section are relatively few. Both the serum and cerebrospinal fluids were positive in twenty cases. From such findings it is clear that the sera in these conditions almost always give a positive result, and the cerebrospinal fluid is negative as an abnormality only. When it is reported, as for instance by Nabarro [34] or by Kirchberg [18], that cases of dementia paralytica frequently give a negative reaction, it must be supposed that some abnormal factor is operating in the series to account for this result.

If the following table be studied, it will be noticed that the cerebrospinal fluid very seldom, if ever, gives a stronger reaction than the serum, in particular when it is remembered that the fluid is used in double quantity and is unheated; thus, since it nearly always reacts less strongly, it will tend to give a negative reaction in rare cases more often than the serum, as is indicated by the published figures. Another factor which probably ensures a more frequent negative reaction in the cerebrospinal fluid is an incorrect diagnosis. It will be allowed that if it is possible to confuse certain cases of syphilitic vascular disease with dementia paralytica, this will account for a negative reaction in the cerebrospinal fluid, while the serum will still be positive, since both conditions are syphilitic. In this connexion the work of Candler [9] is of great interest. In 1909, with Henderson Smith, he tested the cerebrospinal fluid of a number of "general paralytics"; seventy-five of these have now died, and have been examined. Eight cases gave negative reactions during life, and thus only 89 per cent. were positive; but at the autopsy it was found that six of the negative cases were not "general paralytics"; thus in actual fact they had obtained a percentage of 97 positive. This example not only illustrates the fallacies associated with the statistical method in medicine, but also the great difficulty encountered in the diagnosis of dementia paralytica even among the most expert.

The Incidence of the Wassermann Reaction in Dementia Paralytica, &c.

No. of case	Result of first examination	No. of case	Result of first examination
(Juvenile) 16	serum 4.4.4.4.4.	96	serum 4.4.4.4.3.
	cs.f. 4.4.4.4.4.		cs.f. 4.4.4.4.2.
17	4.3.0.0.0.	108	4.4.4.4.0.
	4.2.0.0.0.		4.4.4.4.3.
20	4.4.4.3.1.	(Juvenile) 109	4.4.4.4.4.
	4.4.4.4.1.		4.4.4.4.3.
32	4.4.4.2.1.	119	4.4.4.4.4.
	4.4.4.3.2.		4.4.4.4.4.
33	4.4.4.4.4.	132	4.4.0.0.0.
	4.4.4.0.0.		4.4.4.0.0.
80	4.4.4 3.2.	152	4.4.4.3.1.
	4.4.4.4.4.		4.4.4.0.0.
84	4.4.4.4.4.	165	4.4.3.2.1.
	4.4.4.4.4.		4.4.4.4.0.
90	4.4.4.4.2.	169	4.4.4.4.4.
	4.4.4.4.0.		4.4.4.4.4.
93	4.4.4.4.0.	(Juvenile) 197	4.4.4.4.4.
	4.4.1.0.0.		4.4.4.2.0.
95	4.4.4.3.2.	214	4. - - - -
	4.4.4.3.2.		4.4.4.4.4.

(2) *Tabes Dorsalis, &c.*

In a former study of the literature (1907-1909) we found that 63 per cent. of cases of tabes dorsalis gave a positive reaction in the serum and 32 per cent. in the cerebrospinal fluid. These figures indicate that a positive reaction in both fluids is less constant than in dementia paralytica and that the cerebrospinal fluid fails to give the reaction in a large number of cases. Variety of technique, however, is responsible for divergent results to a larger extent than in dementia paralytica; thus in 1909 Nonne [38] described 50 per cent. positive in the cerebrospinal fluid, while in 1911 [39], he gave 5 to 10 per cent. only positive when using the ordinary test quantities, though with the increased amounts of the "Auswertungsmethode," he obtained practically 100 per cent.

The literature dealing with tabes dorsalis is much smaller than that of dementia paralytica, and in many instances the serum only has been examined.

Our results have been as follows:—

THE INCIDENCE OF THE WASSERMANN REACTION IN TABES DORSALIS, &c.

No. of case	Result of first examination	No. of case	Result of first examination
13	serum 4.4.3.2.1. cs.f. 4.4.4.1.0.	83	serum 2.0 0.0.0. cs.f. 0.0.0.0.0
14	4.4.4.4.4. 4.4. - - -	89	4. - - - - 4. - - - -
23	4.4.4.4.4. 4.3.0.0.0.	112	4.4.4.4.4. 4.4.4.4.4.
27	4.4.4.3.0. 3.1.0.0.0.	117	2.0.0.0.0. 4.4.4.4.1.
30	4.1.0.0.0. 4.4.4.4.0.	131	4.3.2.1.0. 4.4.4.3.1.
37	4.4.2.0.0. 4.4.3.1.0.	142	4.4.4.0.0. 4.4.4.0.0.
46	4.4.4.4.3. 3.0.0.0.0.	143	4.4.4.4.0. 4.4.1.0.0.
55	4.3.1.0.0. 4.4.3.1.0.	144	0.0.0.0.0. 0.0.0.0.0.
56	4.4.4.4.1. 4.4.4.4.1.	145	4.3.2.0.0. 4.4.3.3.0.
58	4.3.1.0.0. 4.4.4.1.0.	150	4.4.4.4.2. 4.4.3.0.0.
67	4.3.2.0.0. 4.4.4.0.0.	186	4.4.3.0.0. 4.4.3.0.0.
70	4.4.4.2.0. 4.3.0.0.0.	200	4.4.4.4.3. 4.4.4.4.4.

Of the twenty-four cases shown above, two were negative in both serum and cerebrospinal fluid (Nos. 83 and 144), while No. 117 was negative in the serum and positive in the cerebrospinal fluid.

On reference to the accounts it will be found that the disease in the two negative cases (Nos. 83 and 144) was quite stationary, although No. 83 had recently developed a Charcot knee. This condition is, however, usually looked upon as trophic and at any rate does not indicate the presence of an active syphilitic lesion. It is probable that in this case the syphilitic process was practically extinct, and in support of this view is the fact that no exacerbation of the reaction occurred after an injection of neo-salvarsan. As regards No. 144 the condition had been stationary for two years and much anti-syphilitic treatment had been applied. In his case, however, the syphilitic process cannot be looked upon as extinct since an injection of neo-salvarsan produced a well-marked "provocative reaction."

This "provocative reaction" was not obtained in the cerebrospinal fluid, and from this fact we conclude that the syphilitic focus which gave rise to it was not "tabetic" since in this case we should have expected some "leakage" into the cerebrospinal fluid.

On the other hand, the negative reaction in the serum of No. 117 and the positive in the cerebrospinal fluid suggests that active lesions in this case were situated in the central nervous system only. The case further supports our contention that the cerebrospinal fluid is relatively stagnant and that substances tend to accumulate in it without passing into the general circulation along the "lymphatic" communications usually described.

The number of cases described is small (24), but it is seen that three negative reactions occurred in the serum and two in the cerebrospinal fluid. These results are consistent with a positive percentage in the serum of 88 and 92 in the cerebrospinal fluid. In tabes dorsalis, however, it is clear that the figures are complicated by factors which probably do not affect dementia paralytica so much. Natural variations in the intensity of the disease or the effects of treatment bear upon the serological result as already clearly shown by Boas [5] in the case of serum. Thus when the reaction is used as a help in the diagnosis of tabes dorsalis, it is essential to notice the activity or otherwise of the disease and also the occurrence of anti-syphilitic treatment, and further, since the reaction may be negative in the serum and positive in the cerebrospinal fluid, it is not enough to examine the former alone.

As regards the strength of the reaction in tabes dorsalis, in particular in the cerebrospinal fluid, it is seen that this on the whole tends to be less than in dementia paralytica, but if it is admitted that weak reactions are common (*c.f.* Nos. 23, 27, 46, 70), it must also be allowed that strong reactions are also frequent. We cannot altogether agree with Nonne [39] therefore when he states that a strong reaction in the cerebrospinal fluid suggests a "great probability of paralysis or tabo-paralysis" and "much less often" of a pure tabes. In our opinion the difference is too inconstant to be of diagnostic importance. Nevertheless a feeble reaction in the cerebrospinal fluid is considerably more common in tabes dorsalis than in dementia paralytica as is also the occurrence of a positive reaction in the cerebrospinal fluid associated with a negative in the serum. In fact it is probable that this combination never occurs in dementia paralytica.

(3) *Cerebrospinal Syphilis.*

The occurrence of the Wassermann reaction in cerebrospinal syphilis has presented problems of the greatest interest.

In the early days of the reaction as applied to neurology, it was generally held that it was not found in the cerebrospinal fluid of these cases and, indeed, a positive reaction in this fluid was held to be strong evidence of "parasyphilis"; thus Mott introduced and still supports a theory in connexion with "parasyphilis" which utilizes this supposed fact in the argument. He states [33]: "Again the observations of Dr. Topley on my hospital cases of cerebral and cerebrospinal syphilis, compared with tabes and general paralysis, entirely conform to Plaut's results. The fluid in cerebrospinal syphilis did not give a positive reaction."

According to Plaut [44] "Both in lues cerebri and in lues spinalis the negative reaction is the rule. . . . This result is found equally in all forms of the disease." Nonne [39] also gives as a typical result in the fluid of cerebrospinal syphilis:—

"(*a*) Originalmethode (0·2 c.c.) positiv in ca. 10 Proz.

"(*b*) Höhere Liquormengen fast stets positiv."

This remark dealing with the larger quantities of test fluid, refers to the "Auswertungsmethode" of Hauptmann and Hössli, which is now generally used in Germany. Instead of 0·2 c.c. of cerebrospinal fluid in a total volume of 3 c.c. in the fixation stage as required by the "original method," this modification utilizes increasing quantities up to 1·0 c.c., and by these means the reaction is found to be almost constant in cerebrospinal syphilis, although this effect is obtained only with the larger quantities.

The results obtained by us in these cases differ in certain respects from those already described. For the purposes of classification we have divided them into two groups. In the first are found those in which the spinal cord was affected, either alone or together with the brain, while in the second those in which the spinal cord was apparently not affected.

INCIDENCE OF THE WASSERMANN REACTION IN CEREBROSPINAL SYPHILIS.

A—Cases in which the cord was apparently affected.

No. of case	Result of first examination	No. of case	Result of first examination
3	serum 4.4.4.4.4. cs.f. 4.4.4.3.2.	102	serum 4.4.0.0.0. cs.f. 4.3.1.0.0.
7	4.4.4.4.4. 0.0.0.0.0.	106	4.4.4.4.4. 4.4.0.0.0.
10	4.4.4.1.0. 4.1.0.0.0.	114	4.2.0.0.0. 4.4.4.4.4.
19	4.4.4.4.4. 4.4.4.3.2.	120	4.2.0.0.0. 4.3.2.0.0.
26	4.4.4.4.4. 4.4 4.0.0.	125	4.4.4.4.4. 4.4.4.4.3.
36	4.4.4.4.2. 4.4.1.0.0.	134	4.4.4.4.0. 4.4.4.4.4.
45	4.4.4.4.4. 4.4.4.4.4.	146	4.4.4.4.4. 4.4.4 4.2.
54	4.4.4.1.0. 0.0.0.0.0.	147	0.0.0.0.0. 4.4.1.0.0.
59	4.4.4 4.4. 4.4.4.4.3.	175	4.4.4.4.4. 4.4.4.4.2.
60	4.4.4.4.4. 4.4.3. - -	177	4.4.4.4.4. 4.4.4.4.0.
64	4.3.2.0.0. 4.4.4.3.1.	182	0.0.0.0.0. 0.0.0.0.0.
74	4.4.4.4.3. 4.4.4.3.1.	189	4.4. - - - 4.4.4.0.0.
77	4.4.4.4.4. 4.4.4.3.0.	199	4.4.4. - - 4.4.4.4.0.
86	4.4.3.3.0. 4.4.4.4.0.	201	4.4.4.4.4. 4.4.4.4.4.
91	4.4.3.0.0. 4.4.4.1.0.	202	4.4.4. - - 4.3.0.0.0.
94	1.0.0.0.0. 4.4.4.3.0.	217	4.4.4.4.0. 4.4.4.4.0.
97	4.4.4.4.4. 0.0.0.0.0.		

B—Cases in which the Brain only was affected.

No. of case	Result of first examination	No. of case	Result of first examination
15	serum 4.4.4.4.0. cs.f. 0.0.0.0.0.	123	serum 0.0.0.0.0. cs.f. 4.4.2.0.0.
39	4.4.4.4.4. 0.0.0.0.0.	128	4.4.4.4.4. 4.1.0.0.0.
44	3.2.0.0.0. 0.0.0.0.0.	133	4.4.4.4.4. 0.0.0.0.0.
53	4.4.4.0.0. 0.0.0.0.0.	148	0.0.0.0.0. 4.2.0.0.0.
61	4.4.4.4.4. 0.0.0.0.0.	149	4.4 4.4.2. 0.0.0.0.0.
62	4.4.2.0.0. 0.0.0.0.0.	156	4.4.4.4.2. 0.0.0.0.0.
73	4.4.4.4.0. 0.0.0.0.0.	158	4.4.4.4.4. 0.0.0.0.0.
85	4.4.4.4.4. 0.0.0.0.0.	159	4.4.4.3.0. 4.4.4.4.1.
92	4.4.4.4.0. 0.0.0.0.0.	161	3.2.0.0.0. 0.0.0.0.0.
104	4.4.4.4.3. 0.0.0.0.0.	170	4.4.4.4.4. 4.4.0.0.0.
107	4.4.3.1.0. 4.2.0.0.0.	183	4.4.4.4.4. 4.4.4.4.4.
110	0.0.0.0.0. 0.0.0.0.0.	204	4.4.4.4.1. 0.0.0.0.0.
111	4.3.1.0.0. 0.0.0.0.0.	205	4.1.0.0.0. 0.0.0.0.0.
122	4.4.4.4.4. 0.0.0.0.0.		

On analysing these figures, it will be found that the number of cases in Group A (cord affected) is thirty-three. The serum gave a positive reaction in all but three cases, Nos. 94, 147 and 182. As regards the last case (No. 182) this negative result is the natural consequence of treatment. The negative reaction in the serum of No. 94 is interesting, being associated with a positive in the cerebrospinal fluid. The case presents several points of similarity with No. 123. In both the examination was made very soon after the onset of the nervous symptoms, and in both the serum subsequently became positive. The results appear to indicate that the syphilitic process was confined to the nervous system, the rest of the body being free as in the case of the so-called "nerve relapses" of the literature. This being the case, the products of the inflammation are first detected in the cerebrospinal fluid and only at a later date do they appear in the blood. If the treatment of the patient is sufficiently intensive, the positive reaction in the serum is only transient.

No. 147 is clinically a very complex case, and the significance of the negative reaction is not clear.

Turning to the cerebrospinal fluids it is seen that four of the thirty-three cases gave a negative reaction. In three of these (Nos. 7, 54, and 182) intensive treatment had been applied, while the other negative case (No. 97) is on the border line between Groups A and B. This case (No. 97) is included among those in which the spinal cord appeared to be affected, on the grounds that the patient exhibited a hyperæsthesia of one thoracic segment which subsequently was associated with muscular wasting. That the lesion was extremely trivial is shown by the presence of only 1 cell per cubic centimetre in the cerebrospinal fluid.[1]

Referring to the effect of treatment shown above, it is necessary to state that in statistics of cerebrospinal cases it is essential to note the existence of anti-syphilitic treatment, since, as will appear later, the reaction in the cerebrospinal fluid in such cases is extremely sensitive to treatment and may rapidly become negative, thus confusing the issue.

Due attention being paid to this question and also to the triviality of the signs in No. 97, it is clear that a positive reaction in the cerebrospinal fluid of patients in whom the spinal cord is affected is a constant phenomenon, as constant even as in dementia paralytica.

Turning to those cases in which the cord was apparently not affected (Group B) twenty-seven in number, it will be seen that three gave a negative reaction in the serum (Nos. 110, 123, and 148), and twenty a negative in the cerebrospinal fluid. No. 123 had been treated originally by salvarsan and the positive reaction in the fluid may be looked upon as a "nerve relapse," as described in the literature; that is, a slight meningo-encephalitis occurring in an almost completely sterilized individual. Since the initial lesion is in the meninges, the positive reaction is detected in the cerebrospinal fluid before it appears in the serum. As regards Nos. 110 and 148, these are both cases of hemiplegia due to cerebral thrombosis, and it is commonly found that such tend to give feeble or negative reactions in the serum. It is clear that a slight thrombotic lesion outside the nervous system might not attract notice, while in the nervous system it will produce marked clinical symptoms. It is possibly this factor which brings a trivial lesion with its accompanying trivial reaction to the notice of the neurologist. In the cerebrospinal fluid also the purely thrombotic cases seldom give a positive reaction, as already noticed by Assmann [2 and 3] and Plaut [44], and this result is no doubt largely due to the fact that the main inflammatory process is confined to the endothelium of the larger vessels, and thus does not affect the pia and occasion an exudate into the sub-arachnoid space. The same factor may also perhaps produce a negative reaction in the cerebrospinal fluid even when the cord is affected by a thrombotic lesion. No. 104, included in Group B, may, on the strength of a slight sphincter lesion, be looked upon as belonging to Group A, the negative reaction in the cerebrospinal fluid being accounted for by a thrombotic lesion.

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[1] We are much indebted to Dr. R. Donald, who made all the cell enumerations mentioned in this work. The method of counting utilizes Donald's technique of measured drops already referred to [11], and not only ensures greater accuracy than a counting chamber but also provides permanent preparations. A small drop of known capacity is deposited on a slide, fixed *in situ* by a superimposed collodion film, stained and counted through by means of a mechanical stage. (*Vide* R. Donald, "Folia Hæmatologica," *Archiv.* [in the press].)

In contradistinction to Group A, the cerebrospinal fluid of cases in Group B relatively seldom gives a positive reaction; there were seven instances only in twenty-seven. Thus, as a rule, the cerebrospinal fluid in purely cerebral cases is negative. The exceptions to the rule, those cases giving a positive reaction in the cerebrospinal fluid, may now be considered. In Nos. 107, 123, 128, and 170, it will be observed that the condition was recent.

No. 148 gave a slight positive reaction but, although at the time of examination he had no sphincter trouble, nevertheless during the original attack this was present, suggesting that there was some affection of the spinal cord.

In No. 159 the reaction of the cerebrospinal fluid is strong although there is little evidence of a lesion of the cord. It is, however, probable that the syphilitic process extended along the medulla, and thus, perhaps, the case should have been included in Group A.

The final example of a positive reaction in the cerebrospinal fluid is No. 183, which resembles No. 59, included in Group A. Both cases differ from all others in being examples of acute encephalitis or perhaps more accurately of acute encephalo-myelitis. The spinal cord was probably involved, but the condition was so recent that no localizing signs had appeared at the time of examination.

It will be seen from the cases described that there is much justification for the division into the two Groups A and B. The cerebrospinal fluid in Group B is almost always negative, and only when the lesion is quite recent is a slight positive reaction found.

The explanation of the difference in the reaction in these two groups probably lies in the fact that the sample of the cerebrospinal fluid examined is derived from the lumbar region. As we have pointed out elsewhere, the sub-arachnoid space in the brain is small, and in fact merely represents a capillary space; there is also no obvious flow of fluid from the brain to the lumbar region and thus constituents of the cerebral fluid will diffuse but slowly into the spinal fluid. It is therefore clear that Wassermann bodies poured into the cerebrospinal fluid directly from a lesion of the spine will be detected more readily than bodies diffusing slowly from the brain.

The strength of the Wassermann reaction in cerebrospinal syphilis (Group A) appears from our tests to be very strong and does not in any way fall short of the reactions found in "parasyphilis." In this respect our results differ from those of Plaut and Nonne. So far as concerns the mere occurrence of the reaction, we agree that in the spinal cases this is constant. We, however, find it to be constant with small quantities of cerebrospinal fluid, while the Hauptmann method obtains this result with large quantities only. We may point out that Stühmer's [54] results are more comparable with ours since, although he obtained a high percentage of positive results with the "Auswertungsmethode," many of his cases were already positive with the smaller quantities of fluid. It is clear that in Nonne's [39] view the strength of the reaction in cerebrospinal syphilis is slight. He states: "If the reaction is positive by the original method (0·2 c.c. of cerebrospinal fluid)," that is if the reaction is strong, "it is highly probable that the case is one of paralysis or tabo-paralysis, much less likely that it is cerebrospinal syphilis or pure tabes."

According to our results this view appears to be untenable. It will be seen that the reaction in the fluid of the spinal cases is at least as constant and as strong as in dementia paralytica, and we therefore dispute the suggestion that either the occurrence of the reaction in the cerebrospinal fluid or its strength has an obvious bearing upon the differential diagnosis between dementia paralytica and cerebrospinal syphilis. If, however, dementia paralytica is capable of being confused with purely cerebral syphilis, then the constant reaction in the former case and the negative in the latter will be of great diagnostic importance.

The differences in the results obtained by Hauptmann's method and our own are presumably due to differences in technique, the most important being in all probability the difference in antigens.

It appears to be quite certain that the advantage of the heart-cholesterin-antigen is particularly apparent in the "cerebral" cases.

It may be argued that the use of this antigen is objectionable since it levels up the diagnostic differences between general paralysis and cerebrospinal syphilis, but to retain these differences by the use of an inferior antigen would be an artificial proceeding and would tend to maintain a fundamental distinction between dementia paralytica and cerebrospinal syphilis which in our opinion does not exist.

(4) *Control Cases.*

In order to ensure the accuracy of the deductions drawn from the preceding cases, we have tested a number of sera and cerebrospinal fluids from patients in whom there was no syphilitic disease of the central nervous system. These controls are divisible into two groups :—

(*a*) Patients with syphilis, but without organic syphilitic disease of the central nervous system. This group will include syphilitic patients with non-syphilitic diseases of the central nervous system.

(*b*) Non-syphilitic patients with disease of the central nervous system.

(*a*) *Syphilitic patients without syphilis of the central nervous system :—*

No. of case	Result of first examination	No. of case	Result of first examination
9	serum 4.4.4.4.4. cs.f. 0.0.0.0.0.	139	serum 4.4.4.3.2. cs.f. 0.0.0.0.0.
29	4.4.4.4.4. 0.0.0.0.0.	154	4.4.4.4.4. 0.0.0.0.0.
35	4.4.4.4.4. 0 0.0.0.0.	155	4.4.4.3.1. 0.0.0.0.0.
38	4.4.4.4.4. 0.0.0 0.0.	166	4.4.4.4.4. 0.0.0.0.0.
63	4.4.4.4.4. 0.0.0.0.0.	171	4.4.4.4.4. 0.0.0.0.0.
68	4.4.4.4.2. 0.0.0.0.0.	178	4.4.4.4.0. 0.0.0.0.0.
78	4.4.4.4 4. 0.0.0.0.0.	187	4.4.4.4.4. 0.0.0.0.0.
79	4 4.4.4.4. 0.0.0.0.0.	196	4. - - - - 0.0.0.0.0.
88	4.2.0.0 0. 0.0.0.0.0.	206	4. - - - - 0.0.0.0.0.
105	4.4 4 4.4. 0.0.0.0.0.	208	2.0.0.0.0. 0.0.0.0.0.
129	4.4.4.2.0. 0.0.0.0.0.	209	0.0.0.0.0. 0.0.0.0.0.
138	4.4.2.1.0 0.0.0.0.0.		

These twenty-three cases include :—

Acute secondary syphilis	6	[Nos. 29; 38; 68; 78; 105; 154.]
Late secondary syphilis..	2	[Nos. 129; 139.]
Symptomless syphilis	7	[Nos. 63; 88; 138; 166; 178; 196; 206.]
Tertiary syphilis	4	[Nos. 35; 79; 155; 171.]
Active congenital syphilis	2	[Nos. 9; 187.]
Inactive congenital syphilis	2	[Nos. 208; 209.]

Except in the case of the two inactive cases of congenital syphilis, the serum was invariably positive and the cerebrospinal fluid negative.

The two negative cases (Nos. 208 and 209) were instances of old congenital syphilis, in which the disease had almost died out. Such cases commonly give a negative reaction. (C.f. J. L. Gordon [15] on the effect of age upon the reaction in congenital syphilis.)

The cases of syphilis without involvement of the nervous system recorded in the literature reacted in a manner similar to ours. Plaut [40] in twenty-seven cases of manifest and latent syphilis found negative reactions in the cerebrospinal fluid in every case, while Boas and Lind [6] obtained the same result in ten. Hauptmann [16] also found no positive reactions in thirteen cases.

The most extensive observations on this subject have, however, been carried out by Altmann and Dreyfus [1], and it appears therefrom that in secondary syphilis, not apparently in the acute stage but after the healing of the chancre, a positive reaction may be found in the cerebrospinal fluid.

	Number of cases	Positive	Negative
Primary syphilis	7	0	7
Primary and secondary syphilis	21	0	21
Secondary syphilis	35	11	24
Tertiary syphilis	2	0	2

Several of these positive reactions were obtained only with high concentrations of cerebrospinal fluid, but, on the other hand, one was positive even with the smallest quantity by the original method.

Similar results have been described by Max Fraenkel [14], who found five cases of secondary syphilis positive in fifteen. These investigations lead us to believe that if we had tested a larger number of cases of late secondary syphilis, positive results might have been encountered. At the same time it is possible that when such cases give a positive result, a very careful clinical examination may reveal actual evidence of an organic lesion in the nervous system. If positive reactions are found in cases in which there is no apparent lesion of the central nervous system, it might be thought that the test loses some of its practical value, since it has been universally held that a positive reaction in the cerebrospinal fluid indicates a syphilitic lesion of the central nervous system. The cases, however, are not really exceptions to the rule, since the positive results are clearly an index of an inflammatory process occurring in the meninges, a view which is also supported by the occurrence of a pleocytosis in the cerebrospinal fluid. From the investigations of Ravaut [47], and among many others of Altmann and Dreyfus, it is seen that a large number of cases of secondary syphilis show marked pathological changes in the cerebrospinal fluid (tension, pleocytosis, increased proteid content); and it is not therefore difficult to assume that a meningitic process is common, and that this in isolated cases may even lead to an exudation of Wassermann substances into the cerebrospinal fluid. Of great theoretical interest also is the case of Zaloziecki [60]. He obtained a positive reaction in a case of tuberculous meningitis occurring in a congenital syphilitic patient, which suggests that the inflammatory exudate derived from the meninges carried with it certain constituents of the blood serum including the Wassermann body, which thus was detectable in the cerebrospinal fluid. The case supports the view that a lesion of the pia mater is necessary for a passage of the reacting body into the fluid.

(*b*) *Non-syphilitic patients with disease of the central nervous system.*—The necessity for these controls lies in the fact that isolated instances of positive reactions in the cerebrospinal fluid have been reported in non-syphilitic conditions, the positive result being alleged to be due to the destruction of nervous tissue and the liberation of lipoids as occurs rarely in the serum as a result of a general anæsthetic. The cases quoted do not in our opinion require extended notice, since the reports of the best technicians have not confirmed them. Hauptmann [16] tested seventy-five cases of non-syphilitic disease of the nervous system, and although some of the patients were syphilitic, no positive reactions were observed.

We have examined examples of the following conditions:—

Old anterior poliomyelitis, Nos. 2, 172.
Neurasthenia, Nos. 4, 41, 174.
Spinal tumour, Nos. 31, 151.
Disseminated sclerosis, Nos. 34, 99, 103, 162, 168.
Cerebral tumour, Nos. 6, 40, 101, 113, 118, 121, 124, 179, 181.
Vascular conditions, Nos. 42, 49, 57, 81, 100, 163, 185, 190.

Syringomyelia, No. 43.
Peripheral neuritis, Nos. 136, 141, 180.
Epilepsy, Nos. 137, 195.
Amyotrophic lateral sclerosis, No. 153.
Subacute combined degeneration of cord, No. 173.
Primary optic atrophy. Pituitary tumour. No. 176.
Congenital ophthalmoplegia interna, No. 191.
Amentia, No. 193.
Acute delusional states, Nos. 194 and 195.

These forty-two cases gave negative reactions both in the serum and in the cerebrospinal fluid. It should be pointed out, however, that the reaction of No. 100 (vascular condition) showed slight inhibition in the cerebrospinal fluid, thus $\frac{\text{serum } 0.0.0.0.0.}{\text{cs.f. } 2.0.0.0.0.}$ This was a case of very slight transient hemiplegia, and although there was no evidence of syphilis obtainable, nevertheless a trivial thrombosis is precisely the form of lesion which might give a negative reaction in the serum and a slight positive in the cerebrospinal fluid. We have retained the case in its present position because 2.0.0.0.0. represents a negative reaction, and there was no other evidence of syphilis. Similarly No. 151 (spinal tumour) gave a reaction $\frac{0.0.0.0.0.}{1.0.0.0.0.}$ but in this case the significance, if any, is not clear.

Summary of the Incidence of the Reaction in Neurological Work.

In *dementia paralytica and tabo-paresis* a strong reaction is practically constant in both serum and cerebrospinal fluid. A negative reaction will make a diagnosis of these conditions highly improbable.

In *tabes dorsalis* the reaction is positive in serum and cerebrospinal fluid, except when the condition has subsided as a result of time or treatment. The strength of the reaction is often not so great as in dementia paralytica; on the other hand, it is often as great.

In untreated *cerebrospinal syphilis* the reaction in the cerebrospinal fluid varies according to the site of the lesion. When the spinal cord is involved it is positive and usually very strong, but when the spinal cord is not involved it is very inconstant and when present weak. The reaction is present most often in recent lesions. In treated cases the reaction is present in the cerebrospinal fluid according to the efficiency or otherwise of the treatment.

In *syphilis* without an organic syphilitic lesion of the central nervous system, the reaction in the cerebrospinal fluid is negative. The occurrence of a reaction in the cerebrospinal fluid, therefore, indicates a syphilitic lesion of the central nervous system.

In *non-syphilitic diseases* of the central nervous system the reaction is negative.

CHAPTER III.—THE EFFECT OF ANTI-SYPHILITIC TREATMENT UPON THE WASSERMANN REACTION.

Introduction.

As first pointed out by Citron the incidence of the Wassermann reaction is dependent largely upon whether anti-syphilitic treatment has or has not been applied; he found that more numerous positive reactions were obtained in those cases of syphilis which had not been treated, than in those which had been treated with mercury. At first, however, the effect of mercury upon the reaction was not generally recognized, chiefly because this substance was seldom successful in turning a positive test into a negative; and it was only on the publication of the quantitative technique of Thomsen and Boas, that it became obvious that a diminution in the strength of the reaction was a constant feature of treatment, even though the fully negative result was not often obtained.

Following the introduction of salvarsan it was found that the reaction could be rapidly influenced in certain cases and, owing to the shorter period of observation necessary, it was possible to estimate with a certain degree of accuracy when the reaction might be expected to become negative. We early found that the effect of intra-muscular injections of salvarsan upon the reaction differed greatly according to the stage of the disease present. Thus according to our results [26], the reaction in primary syphilis usually became negative in five weeks. No case failed to become negative. In secondary syphilis the average was eight weeks and one third of the cases failed to become negative. In early latent syphilis negative reactions were obtained in ten weeks, while in tertiary syphilis only one negative reaction was observed.

From these figures it was clear that the longer the infection had been present, the more difficult was it to obtain a negative reaction.

Later, when intravenous injections were used and a larger total dose, the effect was found to be more definite. The time required to produce a negative reaction in secondary syphilis was slightly reduced, and no case failed to become negative, while in tertiary cases the negative results were more frequent.

With improvements in the technique of the reaction, and particularly with the introduction of the heart-cholesterin antigen, we found that the effect of anti-syphilitic treatment became less obvious in that it required a considerably longer period of time to render certain cases negative. Since the test was very much more searching, it was possible to detect the reacting body in the serum for a longer time than with the older methods. It is therefore necessary to give new average figures according to the technique at present in use.

In discussing the effect of anti-syphilitic treatment we are compelled to confine ourselves to the effect of salvarsan and neo-salvarsan, since we know of no recent records relating to the action of mercury. The exact effect of this latter drug has never been satisfactorily worked out, since research into the question ceased after the introduction of the more potent substances.

THE EFFECT OF TREATMENT UPON THE REACTION IN ACUTE SYPHILIS.

Examples of the Effect of Treatment in Acute Secondary Syphilis.

Case M. L.—Treatment, 2·7 grm. neo-salvarsan in five days.

	Serum
At time of first dose	4.4.4.4.4.
2 *weeks* after first dose	4.4.4.4.4.
4 ———————	4.4.4.4.0.
6 ———————	4.2.0 0.0.
8 ———————	0.0.0.0.0.

Case J. M.—Treatment, 2·0 grm. neo-salvarsan in seven days.

	Serum
At time of first dose	4.4.4.4.4.
2 *weeks* after first dose	4.4.4.4.4.
4 ———————	4.4.4.4.3.
6 ———————	4.4.4.1.0.
8 ———————	4.4.4.2.0.
10 ———————	4.4.0.0.0.
12 ———————	0.0.0.0.0.

Case A. T.—Treatment, 2·4 grm. neo-salvarsan in five days.

	Serum
At time of first dose	4.4.4.4.4.
2 *weeks* after first dose	4.4.4.4.4.
4 ———————	4.4.4.4.4.
6 ———————	4.4.4.4.0.
8 ———————	4.2.0.0.0.
10 ———————	0.0.0.0.0.

We have examined nine cases of acute secondary syphilis at regular short intervals in order to arrive at the shortest time occupied in reducing the positive reaction to negative. The method of treatment was to inject intravenously three doses of neo-salvarsan, within a period of five to ten days. The total dosage varied from 2·0 to 2·7 grm. It was found that the shortest interval before the establishment of a negative reaction was one and a half months and the longest three months. The average of the nine cases was two and a half months. Comparing these results with those formerly obtained by us when using salvarsan and the old Wassermann technique, it is seen that the reaction tends to persist for a slightly longer period with the newer method.

THE EFFECT OF TREATMENT UPON THE REACTION IN TERTIARY SYPHILIS.

In treating cases of tertiary syphilis we soon found that the effect of salvarsan, as measured by the Wassermann reaction, was entirely different compared with the effect in secondary syphilis. Instead of achieving the desired result regularly in a few weeks, we were in many cases unable to detect any diminution in the reaction over a period of many months with the old methods. Sometimes when the reaction was feeble at the outset a negative test with heart-antigen was eventually attained, but in the majority of these the sera were found to give a positive reaction again with the heart-cholesterin antigen. With the methods at present in use we are forced to confess that the production of a negative reaction in tertiary syphilis is a relatively rare phenomenon. Without doubt, however, this result, at any rate in hospital practice, is in part due to the difficulties in dealing with the patients. In almost every case the symptoms rapidly disappear after the first dose, and it is therefore difficult to induce the patients to re-enter the hospital for a chronic intermittent form of treatment. By this method it is, of course, possible to demonstrate a more marked effect of treatment, but even then it is still a question of many months before this is apparent as opposed to a few weeks in the acute stages.

The effect of treatment in the period between the acute secondary and tertiary symptoms depends upon the age of the infection; the earlier cases correspond more to the acute type, while the later tend more towards the tertiary. When the acute stage is passed, however, the reaction soon becomes much more refractory to treatment.

The following cases are examples of the effect of treatment as measured by the present technique.

Examples of the Effect of Treatment in Tertiary Syphilis.

Case A. S.—Treatment, 1·4 grm. neo-salvarsan at first, 0·9 grm. neo-salvarsan at third month.

	Serum
At time of first dose	4.4.4.1.0.
2 *months* after first dose	4.4.1.0.0.
4 ———	4.4.1.0.0.
6 ———	4.3.1.0.0.
8 ———	- - - - -
10 ———	3.2.0.0.0.

Case E. M.—Treatment, 4·2 grm. neo-salvarsan in six months.

	Serum
At time of first dose	4.4.4.4.4.
2 *months* after first dose	4.4.4.4.4.
4 ———	4.4.4.4.4.
6 ———	4.4.4.4.4.
8 ———	4.4.4.4.4.
10 ———	- - - - -
12 ———	4.4.4.3.0.

Case H. G.—Treatment, 1·7 grm. salvarsan in six days.

	Serum
At time of first dose	4.4.4.4.3.
2 *months* after first dose	4.4.4.3.0.
4 ———	4.4.4.0.0.
6 ———	4.4.4.0.0.
8 ———	4.4.4.0.0.
19 ———	4.4.4.4.0.
26 ———	4.4.4.4.0.

The comparatively small effect of anti-syphilitic treatment upon the Wassermann reaction in chronic syphilis might be due to two causes. Firstly, the spirochætes may be readily destroyed and still the reaction may be produced, or, secondly, the spirochætes may not be readily destroyed and thus the reaction may continue. Since it is generally admitted that the phenomenon directly depends upon the presence of the spirochæte, the first assumption may be looked upon as improbable, and particularly when it is remembered that under certain circumstances the spirochætes admittedly avoid destruction. We refer to the relatively frequent occurrence of relapses in the nervous system after an apparently complete cure, showing that spirochætes occupying this position commonly escape a destructive agent in the blood-stream. Again we may refer to the extraordinary frequency of syphilitic affections of the aorta and large vessels. In a series of cadavers taken at random, Turnbull and one of us [P. F.] found that in the great majority of cases in which a positive Wassermann reaction was found, syphilitic mesaortitis was present, often unaccompanied by any other syphilitic lesion. This result suggests that spirochætes lodged in the walls of the large arteries are largely immune to the effect of a spirochæticidal substance in the blood-stream, and this view is supported by the fact that the Wassermann reaction is usually more resistant to treatment in mesaortitis than in any other manifestation of syphilis. So commonly is mesaortitis found in the *post-mortem* room and so resistant are these cases to treatment, that it may almost be said that a chronic case of syphilis, in which the reaction is readily reduced, is unlikely to show mesaortitis, and conversely if no effect can be produced upon the reaction by treatment, the probability of the presence of mesaortitis will be increased.

From these considerations it appears probable that in the chronic cases of syphilis, spirochætes may commonly occupy positions which do not readily come under the influence of treatment. It will then happen that when a case of cutaneous ulceration has been treated, the few spirochætes are destroyed and the lesion healed, but very little effect is observed upon the Wassermann reaction, because another focus in the aorta or central nervous system continues undisturbed the production of the reacting bodies.

The Effect of Treatment upon the Reaction in Syphilis of the Central Nervous System.

Variations in the strength of the Wassermann reaction following anti-syphilitic treatment in diseases of the nervous system do not appear to have been noticed to any great extent.

Plaut (1909) [41] was unable to detect any definite diminution in the reaction in the serum or cerebrospinal fluid in cases of dementia paralytica or even in cerebral syphilis, although in both conditions a great fall in the cell content of the cerebrospinal fluid might occur.

In 1913 Plaut, Rehm and Schottmüller [45] pay very little attention to the question. They state that previously to the introduction of salvarsan, no effect was produced in dementia paralytica by anti-syphilitic treatment; with salvarsan, however, a distinct diminution in the reaction in the cerebrospinal fluid may occur; indeed in rare cases this may become negative.

In general it may be said that anti-syphilitic treatment is not expected to exert any definite beneficial effect upon the reaction in dementia paralytica, while in tabes dorsalis a diminution may be more frequently met with. As regards the behaviour of the reaction in the cerebrospinal forms, it cannot be said that any definite opinion has been expressed.

The failure of the reaction in the cerebrospinal fluid in dementia paralytica to respond to treatment is largely assumed from the work of Plaut in 1909. At the same time it must be pointed out that the intervals between the tests in Plaut's cases were short and were hardly sufficient to allow of the detection of any alteration if it had occurred. Again, it is so little the practice to apply intensive treatment to "general paralytics" that the number of observations is meagre. Further, if such treatment is applied to early cases, it is very difficult to keep them under observation, while in the later asylum cases, little beneficial result can be expected. Thus, on the evidence available, it appears premature to assume that the reaction cannot be diminished in the cerebrospinal fluid of cases of dementia paralytica.

In tabes dorsalis the general opinion upon the effect of treatment is probably deduced from the variable occurrence of the reaction. For instance, if it is relatively common to find stationary cases with negative Wassermann reactions it is not difficult to suppose that these have been produced, at least in part, by treatment. We are, however, unacquainted with any direct demonstration of the effect of anti-syphilitic remedies in tabes dorsalis.

This question would appear to be one of considerable importance, since it must be held that variations in the strength of the reaction in the cerebrospinal fluid are in most cases indications of fluctuations in the intensity of the syphilitic process in the central nervous system. Thus the effect of treatment upon the reaction in the cerebrospinal fluid assumes an important prognostic rôle.

In classifying the results of our investigations we have met with considerable difficulty. As will appear from the works of Dr. Head and Dr. Fearnsides, some cases of "general paralysis" and "tabes dorsalis" when submitted to intensive treatment have behaved in such a manner as to render their inclusion among the group of "parasyphilitics" anomalous. Although by definition and supposed pathology these cases should be incurable, nevertheless the salvarsan injections have in many instances produced a profound amelioration. This fact and certain other considerations have led Dr. Head and Dr. Fearnsides to transfer several cases which might at first sight have been called "general paralysis" and "tabes" to the group of "cerebrospinal syphilis." The diseases dementia paralytica and tabes dorsalis are clinical concepts, and, as we have already pointed out [29], every example does not necessarily fall into the same pathological group. They are not all "parasyphilitic" in the original sense, but some are actively syphilitic, and therefore to group these cases together would produce a clinical rather than a pathological classification.

In the following account of the result of treatment upon the Wassermann reaction we have adopted the clinical classification in order to make our results comparable with those of previous workers; nevertheless it must be clearly stated that from our pathological point of view such a method is incorrect, and, also, in particular cases, may even be unacceptable from the refined clinical standpoint.

Dementia Paralytica and Tabo-paresis.

The effect of treatment upon the Wassermann reaction in dementia paralytica is very difficult to gauge in hospital practice owing to the lack of control over the patients; nevertheless, in the few cases examined we have often found a very material diminution which has corresponded with an improvement in the clinical condition.

When the effect of treatment is to be estimated in disease of the central nervous system, the cerebrospinal fluid only has any direct bearing, since the serum is also under the influence of any other syphilitic focus in the body and may remain unaltered in strength, although the focus in the nervous system, as shown by a negative reaction in the cerebrospinal fluid, has resolved. Thus in order to follow treatment it is essential to perform lumbar puncture periodically, a proceeding which is sometimes resented.

Examples:

Case 32.—[Dementia paralytica].

	Serum	Cerebrospinal fluid	Treatment
At time of first dose	4.4.4.2.1.	4.4.4.3.2.	0·6 grm. salvarsan.
1 *month* after first dose	—	—	0·6 grm. salvarsan.
2 *months*	—	—	
3	—	—	
4	—	—	
5	—	—	
6	—	—	
7	—	—	
8	—	—	
9	—	—	
10	—	—	
11	—	—	
12	—	—	
13	—	—	
14	4.4.4.4.0.	4.4.4.2.0.	

Case 20.—[Tabo-paresis].

	Serum	Cerebrospinal fluid	Treatment
At time of first dose	4.4.4.3.1.	4.4.4.4.1.	1·8 grm. neo-salvarsan
1 *month* after first dose	———	———	
2 *months*	———	———	
3	———	———	
4	4.4.4.1.0.	———	0·9 grm. neo-salvarsan.
5	———	———	
6	———	———	
7	———	———	
8	———	———	
9	———	———	
10	———	———	
11	4.4.4.3.2.	4.4.4.2.0.	

Case 90.—[Tabo-paresis].

	Serum	Cerebrospinal fluid	Treatment
At time of first dose	4.4.4.4.2.	4.4.4.4.0.	2·7 grm. neo-salvarsan.
1 *month* after first dose	———	———	
2 *months*	———	———	
3	———	———	
4	———	———	
5	———	———	
6	4.4.4.4.4.	4.4.3.0.0.	

Case 120.—[Probably encephalitis simulating dementia paralytica].

	Serum	Cerebrospinal fluid	Treatment
At time of first dose	4.2.0.0.0.	4.3.2.0.0.	0·6 grm. salvarsan.
1 *month* after first dose	———	———	
2 *months*	———	———	
3	———	———	
4	———	———	
5	———	———	
6	———	———	
7	———	———	
8	0.0.0.0.0.	0.0.0.0.0.	0·9 grm. neo-salvarsan.
9	———	———	
10	———	———	
11	0.0.0.0.0.	———	

On examination of the four cases illustrated, it will be seen that three (Nos. 20, 90, and 120) showed a definite diminution in the reaction in the cerebrospinal fluid, while the fourth (No. 32) was unaltered. It should be mentioned that Nos. 90 and 120 are no longer looked upon as uncomplicated cases of "parasyphilis," but are now included among the active syphilitic processes.

It would appear from these results that salvarsan treatment is not without effect upon "general paralysis" and "tabo-paralysis" in the ordinary usage of these terms. In some cases, perhaps, the result of treatment may be neglected, but in others it is so marked as to suggest that the pathological process is not identical in all. When the effect of treatment is most pronounced, it is often found that there is evidence of an active involvement of the meninges, that is to say, such cases appear to be transitional forms between the true dementia paralytica and cerebrospinal syphilis in the sense of our previous publication [29]. In pure "parasyphilis" we assume a lesion practically confined to the nerve structures and resistant to treatment. In most cases of "parasyphilis," however, the lesion is not so restricted, and actively involves the vascular structures. This element of "parasyphilis" will be curable.

Tabes Dorsalis.

Since the Wassermann reaction in tabes dorsalis may be found to be negative, it might be expected that treatment in these cases would have a greater effect than in dementia paralytica. We have, however, been unable to demonstrate any marked difference, as the following examples will show. When the anti-syphilitic treatment consists only of mercury, it is true that after a prolonged period a diminution may be found in tabes dorsalis, while none is evident in dementia paralytica. This result, however, is largely due to the early death of the "paralytic" before mercury has had time to reduce the disease to a state of chronicity as in tabes dorsalis.

Examples :

Case 37.—

	Serum	Cerebrospinal fluid	Treatment
At time of first dose	4.4.2.0.0.	4.4.3.1.0.	0·9 grm. neo-salvarsan.
1 *month* after first dose	—	—	0·9 grm. neo-salvarsan.
2 *months*	4.3.2.0.0.	—	
3	—	—	
4	—	—	
5	4.4.4.2.0.	—	
6	—	—	
7	4.4.4.2.0.	4.4.2.0.0.	0·9 grm. neo-salvarsan.
8	—	—	
9	—	—	
10	—	—	
11	4.4.4.2.0.	4.4.2.0.0.	

Case 150.—

	Serum	Cerebrospinal fluid	Treatment
At time of first dose	4.4.4.4.2.	4.4.3.0.0.	2·7 grm. neo-salvarsan.
1 *month* after first dose	—	—	
2 *months*	—	—	
3	—	—	
4	—	—	
5	—	—	
6	—	—	
7	—	—	
8	—	—	
9	—	—	
10	—	—	
11	4.4.4.4.4.	4.4.1.0.0.	

Case 125.—

	Serum	Cerebrospinal fluid	Treatment
At time of first dose	4.4.4.4.3.	4.4.4.4.3.	2·7 grm. neo-salvarsan.
1 *month* after first dose	———	———	
2 *months* ———	4.4.4.4.1.	———	
3 ———	4.4.4.4.4.	4.4.4.0.0.	0·3 grm. neo-salvarsan.
4 ———	4.4.4.4.2.	———	2·2 grm. neo-salvarsan.
5 ———	4.4.4.4.1.	———	
6 ———	4.4.4.4.2.	———	
7 ———	———	———	
8 ———	4.4.4.4.0.	4.4.2.0.0.	

Cases Nos. 37 and 150 were both classical examples of tabes dorsalis, and the treatment administered resulted in no obvious alteration in the reaction. In No. 125, however, a very material improvement resulted, and this coincided with a clinical improvement. This case has been transferred to the cerebrospinal syphilis group owing to evidence of an active meningeal lesion, and probably represents a transitional form between the pure uncomplicated "tabes" and those "active" lesions which do not primarily involve the nerve-tissues proper.

We conclude, therefore, from these results that anti-syphilitic treatment is almost without effect upon the pure "parasyphilitic" tabes dorsalis, as also upon the pure dementia paralytica; but in a number of cases diagnosable as "tabes," or "general paralysis," treatment has a very definite effect, and such cases show clinical evidence of an associated interstitial syphilis.

It should be noticed that although treatment has little or no effect upon the reaction in the pure "parasyphilitic" cases, this result cannot be looked upon as in any way characteristic of this condition. We have already shown that in many cases of pure tertiary syphilis, treatment is apparently abortive; thus it cannot strictly be said that "parasyphilis" is any more incurable than tertiary syphilis. If the index of "cure" is taken to be the disappearance of clinical symptoms, the difference between the course of "parasyphilis" and tertiary syphilis is marked; but, judging the Wassermann reaction to be a measure of the effect upon the virus, it is seen that the apparent effect of treatment in tertiary syphilis is largely illusive. At any rate, the difference is purely one of degree, and it is too slight to support the view that "parasyphilis" is a condition distinct from syphilis.

Cerebrospinal Syphilis.

Turning to those cases in which the syphilitic process is usually described as being "active" as opposed to "parasyphilitic," we find that the effect of treatment is very much more marked; indeed, in most cases the reaction in the cerebrospinal fluid may readily be reduced to negative.

Example of acute cerebrospinal syphilis:

Case 59.—

	Serum	Cerebrospinal fluid	Treatment
At time of first dose	4.4.4.4.4.	4.4.4.4.3.	1·8 grm. neo-salvarsan.
1 *month* after first dose	4.4.4.4.4.	4.4.4.1.0.	0·9 grm. ,,
2 *months*	4.4.4.4.3.	4.4.3.0.0.	0·9 grm. ,,
3	———	———	
4	———	———	
5	4.4.1.0.0.	0.0.0.0.0.	0·9 grm. ,,
6	1.0.0.0.0.	———	0·9 grm. ,,
7	———	———	
8	———	———	
9	———	———	
10	———	———	
11	———	———	
12	2.0.0.0.0.	———	

In this case of acute cerebrospinal syphilis the onset of the condition was seven months after infection, the patient being in the secondary stage. He had undergone six months' mercurial treatment. It will be seen that the salvarsan injections had a rapid effect upon the cerebrospinal fluid, which was found to be negative after five months. The serum was also quickly reduced to normal, although the effect was not so prompt as in the cerebrospinal fluid.

Examples of chronic cerebrospinal syphilis:

Case 19.—

	Serum	Cerebrospinal fluid	Treatment
At time of first dose	4.4.4.4.3.	4.4.4.3.2.	1·5 grm. neo-salvarsan.
1 *month* after first dose	———	———	
2 *months*	———	———	
3	———	———	
4	———	———	
5	———	———	
6	———	———	
7	———	———	
8	4.4.4.4.3.	———	
9	4.4.4.4.3.	0.0.0.0.0.	0·9 grm. neo-salvarsan.

Case 74.—

	Serum	Cerebrospinal fluid	Treatment
At time of first dose	4.4.4.4.2.	4.4.4.3.1.	2·7 grm. neo-salvarsan.
1 *month* after first dose	———	———	
2 *months*	———	———	
3	———	———	
4	4.4.4.3.0.	———	
5	———	———	
6	———	———	
7	———	———	
8	4.4.4.3.0.	0.0.0.0.0.	

Case 134.—

	Serum	Cerebrospinal fluid	Treatment
At time of first dose	4.4.4.4.0.	4.4.4.4.4.	0·6 grm. salvarsan.
1 *month* after first dose	———	———	0·9 grm. neo-salvarsan.
2 *months* ———	4.4.4.4.4.	———	
3 ———	———	———	
4 ———	4.2.1.0.0.	4.2.0.0.0.	0·9 grm. neo-salvarsan.

Case 146.—

	Serum	Cerebrospinal fluid	Treatment
3 *months* before first dose	4.4.4.4.4.	4.4.4.4.2.	
2 *months* ———	———	———	
1 *month* ———	———	———	
At time of first dose	———	———	1·8 grm. neo-salvarsan.
1 *month* after first dose	———	———	
2 *months* ———	———	———	
3 ———	———	———	
4 ———	4.4.3.2.0.	4.1.0.0.0.	0·9 grm. neo-salvarsan.

From the few examples detailed above it is clear that the positive reaction in the cerebrospinal fluid of cases of acute and chronic syphilis of the central nervous system is rapidly influenced by specific treatment, although the serum in the latter condition is less affected, as in chronic syphilis elsewhere. When it is remembered that the reaction in the cerebrospinal fluid of pure "parasyphilis" is little affected by treatment, while in cerebrospinal syphilis the effect is pronounced, it would appear that the result of treatment may be taken as some *indication of the presence or absence of "parasyphilis."* If, after sufficient treatment the reaction in the cerebrospinal fluid rapidly diminishes, the probability is greatly in favour of a lesion mostly lymph-vascular, and thus the prognosis is much better than when the reaction is found to be resistant to treatment. In the latter case the presence of a "parasyphilitic" nerve lesion is to be suspected and the prognosis should be guarded.

The reason for the relative futility of treatment in the "parasyphilitic" conditions is doubtful. According to some, the source of the reacting substance in "parasyphilis" is the degenerating nerve-cell, and since this degeneration is progressive, the supply of reacting substance will be continuous and unaffected by treatment. This explanation is, however, highly improbable. The origin of the reacting substance everywhere is the specific activity of the *Spirochæta pallida* exerted upon the neighbouring cells. When the nerve-cells are intoxicated by this organism, they no doubt give rise to a quantity of reacting substance, but the subsequent degeneration has in it no syphilitic element and no specific bodies will be liberated.

We consider that the more probable explanation for the lack of effect in "parasyphilis" and the marked effect in syphilis, is that the focus of origin of the reacting substance in the former case is not resolved by treatment, while in the latter it rapidly disappears. Cerebrospinal syphilis is a lesion chiefly or entirely confined to the lymph-vascular tissues of the brain and practically always involves the meninges. The products of this inflammation including the Wassermann substance appear in the cerebrospinal fluid as an exudate from the surrounding meninges, and thus if the inflammatory process is resolved by treatment the local production of Wassermann substances will rapidly cease. If comparison may be made with active syphilitic lesions elsewhere, it is probable that a gummatous meningitis may be entirely healed in a few days, and thus the arrest of reacting bodies will be sudden; nevertheless in practice it is always found that the reaction persists for several months and gradually diminishes in strength, and, in our view, this is due merely to the stagnation of the cerebrospinal fluid.

If, therefore, the behaviour of the cerebrospinal fluid after treatment of cerebrospinal syphilis is readily explicable, the same cannot be said of "parasyphilis." In this condition the syphilitic process persists and therefore it is clear that the *Spirochæta pallida* must persist in spite of treatment. This phenomenon might be due to the development of a resistant strain of spirochætes, when treatment throughout has been by the same drug, but it would not explain the futility of salvarsan, when a patient had previously been treated by mercury. It may also be said that the assumption of a resistant strain of spirochætes is not supported by much experimental evidence.

A more probable explanation of the failure of treatment to destroy the spirochæte is to be found in the case described by us in 1911 [27]. An infant which died after salvarsan treatment was found to have arsenic in all the organs examined with the exception of the brain, and from this it may be deduced that arsenic does not penetrate to the substance of the brain. Such an occurrence would of course account for the survival of spirochætes situated in the brain-tissue proper, as in "parasyphilis," and for the continuation of the supply of Wassermann substances. Since, however, the passage of these substances into the cerebrospinal fluid depends upon a pathological alteration of the pia mater, it might be objected that the alteration present in "parasyphilis" should be resolved and the exudation of Wassermann bodies prevented. On the other hand, the affection of the meninges in pure "parasyphilis" is not a primary process due to the *Spirochæta pallida* locally, but is secondary to the micro-organism lying in the nerve-tissues at a distance; thus the infiltration of the pia will persist so long as the spirochæte persists, in spite of the fact that the arsenic may have free access to the meninges.

THE EFFECT OF TREATMENT IN PRODUCING EXACERBATIONS OF THE REACTION.

It has long been recognized that injections of salvarsan or mercurial inunctions sometimes produce an exacerbation of the Wassermann reaction, so that it may become positive when before treatment it was negative, or there may be a quantitative increase in a previously positive reaction. Since the introduction of salvarsan these exacerbations have become more common, and the word "provocative" has been applied to an injection which produces this result. The phenomenon has considerable theoretical interest, and also, to a certain extent, a practical value, especially in neurology.

The practical utility of a "provocative" injection lies in its intentional application in order to produce a positive reaction in a suspected case of syphilis, in which it was previously negative. Thus the "provocative" injection may have considerable diagnostic value.

Further, it has been laid down that if an individual with a negative reaction, but known to have had syphilis previously, does not show an exacerbation of the Wassermann reaction as a result of an injection of salvarsan, he may be looked upon as being cured.

In our opinion this latter assumption is without sufficient foundation; the only deduction to be made from such an occurrence is that at the time of the injection the individual had no active syphilitic lesion, but it does not preclude the possibility of an exacerbation or relapse of syphilis at a later date.

In order to disclose an exacerbation after a "provocative" injection, it is advisable to test the reaction more than once, since the time of its occurrence cannot be accurately foretold. Suitable periods are one and two weeks after the injection, but if only one test is to be made, this may be applied ten days after.

It is important that only one dose be given, since a repetition of the injection may abort an exacerbation before it has developed sufficiently to be detectable.

Examples of "provocative" reactions :

Case 144.—Stationary tabes dorsalis.

		Serum	Cerebrospinal fluid
10.7.1912	—	0.0.0.0.0.	0.0.0.0.0.
16.7.1912	—	- - - - -	0.0.0.0.0.
18.7.1912	Injection 0·6 grm. neo-salvarsan	0.0.0.0.0.	- - - - -
20.7.1912	—	0.0.0.0.0.	- - - - -
22.7.1912	—	0.0.0.0.0.	- - - - -
24.7.1912	—	- - - - -	0.0.0.0.0.
25.7.1912	—	1.1.0.0.0.	- - - - -
29.7.1912	—	- - - - -	0.0.0.0.0.
30.7.1912	—	4.4.4.1.0.	- - - - -
1.8.1912	Injection 0·9 grm. neo-salvarsan	- - - - -	- - - - -
7.8.1912	—	4.4.4.3.1.	1.0.0.0.0.
10.8.1912	Injection 0·9 grm. neo-salvarsan	- - - - -	- - - - -
8.10.1912	—	0.0.0.0.0.	0.0.0.0.0.
14.10.1912	Injection 0·6 grm. neo-salvarsan	- - - - -	- - - - -
23.10.1912	—	0.0.0.0.0.	- - - - -

A "provocative" reaction appeared in the serum, but not in the cerebrospinal fluid seven to twelve days after the injection.

Case 94.—Cerebrospinal syphilis.

		Serum	Cerebrospinal fluid
16.10.12	—	0.0.0.0.0.	4.4.4.3.0.
21.10.12	Injection 0·9 grm. neo-salvarsan	- - - - -	- - - - -
30.10.12	—	0.0.0.0.0.	- - - - -
31.10.12	Injection 0·9 grm. neo-salvarsan	- - - - -	- - - - -
2.11.12	—	0.0.0.0.0.	- - - - -
5.11.12	—	0.0.0.0.0.	4.4.4.3.0.
17.1.13	Injection 0·9 grm. neo-salvarsan	- - - - -	- - - - -
22.1.13	—	4.3.2.0.0.	- - - - -
23.4.13	—	1.0.0.0.0.	0.0.0.0.0.

In this case no "provocation" of the reaction occurred within nine days of the first dose, although the patient was clearly syphilitic. The reaction in the serum subsequently became positive, but it is doubtful whether this was due to the injection given five days before.

Case 106.—Cerebrospinal syphilis.

		Serum	Cerebrospinal fluid
24.1.12	—	4.4.4.4.4.	4.4.0.0.0.
27.1.12	Injection 0·6 grm. salvarsan	- - - - -	- - - - -
31.1.12	Injection 0·6 grm. salvarsan	- - - - -	- - - - -
20.3.12	—	4.3.3.2.0.	- - - - -
9.7.12	Injection 0·6 grm. salvarsan	- - - - -	- - - - -
10.7.12	—	0.0.0.0.0.	0.0.0.0.0
17.7.12	—	4.3.0.0.0.	- - - - -

A "provocative" reaction occurred seven days after the injection.

Case 110—Hemiplegia.

		Serum	Cerebrospinal fluid
10.1.12	Mercurial inunctions	0.0.0.0.0.	0.0.0.0.0.
7.2.12		4.3.0.0.0.	- - - - -

An example of the "provocative" effect of mercury.

The value of the "provocative" injection for diagnostic purposes is probably greater in neurology than in general syphilitic work, because in this branch there are more conditions resulting from very trivial lesions which may fail to give a Wassermann reaction at first. Further, the central nervous system is a situation commonly occupied by the spirochæte while in a latent condition. Thus in neurology this test may have a certain value, but at the same time it must not be forgotten that it is often abortive.

The phenomenon is probably of a similar nature to the "Herxheimer reaction" or to "spirochæte fever," that is to say, it is probably due to the sudden destruction of a focus of spirochætes, and thus a sudden intoxication of the neighbouring cells by liberated "toxins." This would have the effect not only of producing a quantity of Wassermann substances locally, but it might also disturb the balance between virus and cell, so that the former might be enabled to pass into a greater state of activity.

Variations in the Reaction without Treatment.

We have already described the diminution or exacerbation of the Wassermann reaction which may occur after anti-syphilitic treatment; but it is also found that such variations occur without any treatment having been applied. The effect of an anti-syphilitic drug is to cure the symptoms of the disease by destroying the spirochæte, and thus the reaction becomes negative; but the spirochæte may be destroyed, and the symptoms healed by the natural protective processes without any active medical intervention, in exactly the same manner as may occur in other infective conditions.

This is the explanation of the spontaneous healing of the secondary symptoms and the gradual diminution of the Wassermann reaction which may occur in the entire absence of anti-syphilitic treatment. The common finding of a negative reaction in stationary tabes is also an example; the syphilitic process has died out spontaneously.

We have been able to record this phenomenon in cases in which treatment had been omitted on the grounds that the patients were "parasyphilitic."

Case 142.—Tabes dorsalis.

14.12.11	..	serum	4.4.4.1.0.	Cells in cs.f. = 21 per c.mm.
		cs.f.	4.4.4.0.0.	
7.5.13	..	serum	4.4.4.4.2.	Cells in cs.f. = 6 per c.mm.
		cs.f.	4.4.1.0.0.	

Case 86.—Dementia paralytica (later classed as cerebrospinal syphilis).

13.3.12	..	serum	4.4.3.3.0.	Cells in cs.f. = 63 per c.mm.
		cs.f.	4.4.4.4.0.	
16.4.13	..	serum	4.4.4.4.4.	
		cs.f.	4.4.0.0.0.	Cells in cs.f. = 19 per c.mm.

In these two cases the decrease in the reaction in the cerebrospinal fluid suggested a certain degree of improvement in the local nervous condition, and in one (No. 86) this view was supported by a marked amelioration in the clinical state. Variations in the reaction in the opposite direction, that is, spontaneous exacerbations, are, of course, common and indicate a relapse, and of this many examples might be quoted. If the blood-test is performed sufficiently often it will be found that the relapse of the Wassermann reaction nearly always precedes a clinical relapse by several weeks or months, and thus the occurrence of the latter may be prevented by suitable treatment.

A relapse occurring in the central nervous system, however, presents some details of interest; thus in the great majority of cases, its effect is apparent in the cerebrospinal fluid before the serum. This result might be expected since the reacting substances are poured directly into the cerebrospinal fluid as an exudate and are only detectable in the serum, when they have accumulated in sufficient quantity. It is for this reason that the cases exhibiting a "nerve relapse" often yield a negative reaction in the serum.

In the following case, No. 123, the patient was examined experimentally merely because of the occurrence of headaches within two years of infection. He was found to have a positive Wassermann reaction in the cerebrospinal fluid and a great increase in the cell-content, although the serum was negative and no physical signs of disease were manifest. In this case the lesion was detected by the reaction before the onset of signs and the serum became positive at a later date only. The attack aborted as the result of intensive treatment as shown by the decreasing reaction in the cerebrospinal fluid and the reduction of the cell-content to normal.

Case 123.—Late Secondary Syphilis with Relapsed Meningo-encephalitis.

		Serum	Cerebrospinal fluid	
25-30.11.1911	Injection 1·2 grm. salvarsan	- - - - -	- - - - -	Superficial ulceration of tongue fourteen months after infection. Twelve months Hg.
3.4.1912	———	4. - - - -	- - - - -	
13.11.1912	———	1.0.0.0.0.	- - - - -	Headaches.
28.11.1912	Injection 0·9 grm. neo-salvarsan	0.0.0.0.0.	4.4.1.0.0. 85 cells per c. mm.	No nervous symptoms.
4.6.1913	———	4.4.4.4.2.	4.4.4.4.3. 90 cells per c.mm.	Headaches. Mental irritability. No physical signs.
6.6.1913	Injection 0·6 grm. neo-salvarsan			
12.6.1913	Injection 0·9 grm. neo-salvarsan			
18.6.1913	Injection 0·9 grm. neo-salvarsan			
23.6.1913	Injection 0·9 grm. neo-salvarsan			
26.7.1913	Injection 0·9 grm. neo-salvarsan			
31.7.1913	———	4.4.4.3.0.	- - - - -	
13.8.1913	———	4.3.2.0.0.	4.4.4.0.0. 3 cells per c.mm.	
19.9.1913	———	4.4.3.0.0.	- - - - -	
19.11.1913	———	0.0.0.0.0.	- - - - -	

It will be noticed that the patient escaped observation for six months after a single dose of neo-salvarsan. This dose probably alleviated the headaches but did not materially hinder the development of the disease. On his return he was found to be in a condition worse than before. This is the phenomenon often described as a "nerve relapse," and is sometimes erroneously ascribed to the salvarsan injection, instead of to the progress of the disease after insufficient treatment.

The following case also illustrates the exacerbation of the reaction in the serum; the cerebrospinal fluid was not tested, and therefore it is not known whether this became positive before the symptoms appeared. The exacerbation was transient and subsided without treatment.

Case 91.—Cerebrospinal syphilis.

		Serum	Cerebrospinal fluid	
10.7.1912	Injection 0·6 grm. salvarsan	4.4.3.0.0.	4.4.4.0.0.	
17.7.1912	Injection 0·6 grm. salvarsan	- - - - -	- - - - -	
15.1.1913	Injection 0·9 grm. neo-salvarsan	3.2.1.0.0.	1.0.0.0.0.	
22.1.1913	———	3.2.1 0.0.	- - - - -	
18.6.1913	———	3.0.0.0.0.	- - - - -	Onset of herpes zoster
25.6.1913	———	4.3.0.0.0.	- - - - -	
26.8.1913	———	0.0.0.0.0.	- - - - -	

CHAPTER IV.—CONCLUSIONS.

Before estimating the value of a report upon a Wassermann test, the physician should be acquainted with the methods and general results of the serologist who gives the report.

From the results of the technique described above, the following general conclusions may be drawn:—

(1) In general diagnostic work, exclusive of nervous conditions, a positive reaction is so constant in active syphilis that such a diagnosis, made in the face of a negative result, will require very special support on other grounds before it can be considered probable.

(2) A positive reaction in the cerebrospinal fluid indicates a syphilitic lesion of the central nervous system.

(3) In active untreated cases of dementia paralytica, tabes dorsalis, and cerebrospinal syphilis, the reaction is positive both in the serum and cerebrospinal fluid. In cerebral syphilis, without involvement of the spinal cord, the cerebrospinal fluid is usually negative. Except in the latter cases the strength of the reaction has no certain diagnostic value.

(4) The reaction is apt to be negative in the serum or cerebrospinal fluid in cases of hemiplegia, non-progressive tabes dorsalis, and old lesions of the nervous system, especially in cases of stationary congenital syphilis. It is also usually negative in the serum particularly in very recent nerve lesions of the late secondary period, and in the cerebrospinal fluid particularly in treated cerebrospinal cases.

(5) The occurrence of a positive reaction in one of the test-fluids when the other is negative is so common that a reaction found negative in one fluid only is insufficient to exclude syphilis.

(6) Pure "parasyphilitic" lesions do not respond satisfactorily to treatment as shown by the slight effect upon the reaction in the cerebro-

spinal fluid. Cerebrospinal lesions react very readily to treatment. The celerity with which the reaction in the cerebrospinal fluid responds to treatment is an index of the "parasyphilitic" or "syphilitic" nature of the case.

(7) The positive reaction in the serum is rapidly made negative by treatment in acute syphilis; but in chronic syphilis this effect is produced very slowly. In the cerebrospinal fluid, on the other hand, the rate of reduction of the reaction does not depend upon the duration of the infection. Thus, in gummatous lesions of the central nervous system, as also in acute secondary cerebrospinal syphilis, the effect of treatment upon the reaction in the cerebrospinal fluid is rapid.

(8) The "provocative" injection of salvarsan for the purpose of exciting an exacerbation of the reaction has some, but probably an exaggerated, diagnostic value.

REFERENCES.

[1] ALTMANN, K., und DREYFUS, G. L. *Münch. med. Wochenschr.*, 1913, S. 464 und 531.

[2] ASSMANN, H. *Deutsche med. Wochenschr.*, 1911, S. 1603 und 1648.

[3] *Idem.* *Deutsche Zeitschr. f. Nervenheilk.*, 1910, Bd. xl, S. 131.

[4] BOAS, H. *Berl. klin. Wochenschr.*, 1909, S. 400.

[5] *Idem.* "Die Wassermannsche Reaktion," Berlin, 1911, S. 94.

[6] BOAS, H., und LIND, H. *Zeitschr. f. d. ges. Neurol. u. Psychiat.*, Orig., 1911, Bd. iv, S. 689.

[7] BROWNING, C. H., CRUICKSHANK, J., and MACKENZIE, I. *Biochem. Zeitschr.*, 1910, Bd. xxv, S. 85.

[8] *Idem.* *Journ. of Path. and Bact.*, 1910, vol. xiv, p. 484.

[9] CANDLER, J. P. *Lancet*, 1911, vol. ii, p. 1320.

[10] DEMBOWSKI, H. *Deutsche med. Wochenschr.*, 1911, S. 1651.

[11] DONALD, R. *Proc. Roy. Soc.*, B., 1913, vol. lxxxvi, p. 198.

[12] EISENBERG, P., und NITSCH, R. *Zeitschr. f. Immunitätsforsch.*, Orig., 1909, Bd. iii, S. 376.

[13] FACCHINI, *Zeitschr. f. Immunitätsforsch.*, 1909, Bd. ii, S. 257.

[14] FRAENKEL, M. *Zeitschr. f. d. ges. Neurol. u. Psychiat.*, 1912, Bd. xi, S. 1.

[15] GORDON, J. L. *Lancet*, 1913, vol. ii, p. 861.

[16] HAUPTMANN, A. *Deutsche Zeitschr. f. Nervenheilk.*, 1911, Bd. xlii, S. 240.

[17] HAUPTMANN und HÖSSLI, H. *Münch. med. Wochenschr.*, 1910, S. 1581.

[18] KIRCHBERG, P. *Archiv f. Psychiat.*, 1913, Bd. l, S. 621.

[19] KOLLE, W., und STINER, O. *Deutsche med. Wochenschr.*, 1911, S. 1739.

[20] LANDSTEINER, K., MÜLLER, R., und PÖTZL, O. *Wien. klin. Wochenschr.*, 1907, S. 1565.

[21] LESSER, F. *Berl. klin. Wochenschr.*, 1909, S. 974.

[22] LEVADITI, C., et YAMANOUCHI, T. *Compt.-rend. de la Soc. de Biol.*, 1907, t. lxiii, p. 740.

[23] McINTOSH, J., and FILDES, P. "Syphilis from the Modern Standpoint," London, 1911, p. 117.

[24] *Idem.* *Op. cit.*, pp. 123 *et seq.*

[25] *Idem.* *Op. cit.*, p. 143.

[26] *Idem.* *Op. cit.*, p. 159.

[27] *Idem.* *Op. cit.*, p. 220.

[28] *Idem.* *Zeitschr. f. Chemotherapie*, Orig., 1912, Bd. i, S. 79.

[29] *Idem.* *Lancet*, 1913, vol. ii, p. 921.

[30] Marie, A., et Levaditi, C. *Annales de l'Institut Pasteur*, 1907, t. xxi, p. 138.
[31] Meier, G., und Mayer, H. "Die neuen Methoden der Syphilisdiagnose und Syphilistherapie," Freiburg i. B., 1911.
[32] Michaelis. *Berl. klin. Wochenschr.*, 1908, S. 667.
[33] Mott, F. W. *Trans. XVII. Internat. Cong. of Medicine*, London, 1913 (Section of Neuropathology), pt. i, p. 273.
[34] Nabarro, D. *Brit. Med. Journ.*, 1912, vol. ii, p. 1454.
[35] Noguchi, H. "Serum Diagnosis of Syphilis." Philadelphia and London, 1910.
[36] *Idem.* *Journ. of Exp. Med.*, 1909, vol. xi, p. 84.
[37] Noguchi, H., and Bronfenbrenner, J. *Journ. of Exp. Med.*, 1911, vol. xiii, p. 43.
[38] Nonne, M. "Syphilis und Nervensystem," Berlin, 1909, S. 634.
[39] *Idem.* *Deutsche Zeitschr. f. Nervenheilk.*, 1911, Bd. xlii, S. 201.
[40] Plaut, F. "Die Wassermannsche Serodiagnostik der Syphilis," Jena, 1909, S. 43.
[41] *Idem.* *Op. cit.*, S. 173.
[42] *Idem.* *Zeitschr. f. d. ges. Neurol. u. Psychiat.*, Orig., 1911, Bd. iv, S. 39.
[43] Plaut, F., Rehm, O., und Schottmüller, H. "Leitfaden zur Untersuchung der Zerebrospinalflüssigkeit," Jena, 1913, S. 28.
[44] *Idem.* *Op. cit.*, S. 136.
[45] *Idem.* *Op. cit.*, S. 142.
[46] Porges, O., und Meier, G. *Berl. klin. Wochenschr.*, 1908, S. 731.
[47] Ravaut, P. *Bull. et Mém. de la Soc. méd. des Hôpitaux de Paris*, 1903, t. xx, p. 1026.
[48] Ritz, H., und Sachs, H. *Deutsche med. Wochenschr.*, 1912, S. 2009.
[49] Sachs, H. *Berl. klin. Wochenschr.*, 1911, S. 2066.
[50] Sachs, H., und Altmann, K. *Berl. klin. Wochenschr.*, 1908, S. 494.
[51] *Idem.* *Ibid.*, 1908, S. 699.
[52] Sachs, H., und Rondoni, P. *Zeitschr. f. Immunitätsforsch.*, Orig., 1909, Bd. i, S. 132.
[53] *Idem.* *Berl. klin. Wochenschr.*, 1908, S. 1968.
[54] Stühmer, A. *Centralbl. f. Bakt.*, Orig., 1912, Bd. lxi, S. 171.
[55] Thomsen, O. *Zeitschr. f. Immunitätsforsch.*, Orig., 1910, Bd. vii, S. 389.
[56] Thomsen, O., und Boas, H. *Zeitschr. f. Immunitätsforsch.*, 1911, Bd. x, S. 337.
[57] *Idem.* *Ibid.*, 1913, Bd. xviii, S. 516.
[58] Walker, I. C., and Swift, H. F. *Journ. of Exp. Med.*, 1913, vol. xviii, p. 75.
[59] Weil, E., und Kafka, V. *Med. Klinik.*, 1911, S. 1314.
[60] Zaloziecki, A. *Archiv f. Hygiene*, 1913, Bd. lxxx, S. 196.

ON THE BULBAR NUCLEI, WITH SPECIAL REFERENCE TO THE EXISTENCE OF A SALIVARY CENTRE IN MAN.

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ANATOMICAL observations in man and experimental investigations in the lower animals have provided us with an extensive knowledge of the position and relations of the nuclei of the cranial nerves in the medulla oblongata. The following paper, based upon a case which afforded unusual facilities for such an investigation, cannot claim to do more than confirm our previous knowledge of these nuclei; an attempt, however, will be made to go further and establish the existence of a salivary centre in the medulla oblongata.

Experimental researches of Kohnstamm and Yagita [2, 3, 5, 6] have demonstrated the presence of a salivary centre in the medulla in dogs. These results were obtained by division of the chorda tympani and the nerves to the submaxillary and parotid glands. It is seldom that opportunity is afforded in man of studying the effects of lesions which in their nature and result approximate to those of experimental nerve division in the lower animals. But in July, 1913, a brain and spinal cord were received at the Neurological Institute, Frankfurt-am-Main, from a patient where the isolated character of the lesions reproduced experimental conditions with unusual accuracy. A fracture of the base of the skull inflicted local injury upon the trunks of the vagus, glossopharyngeal, spinal accessory, and hypoglossal nerves, without any lesion in the brain itself. Examination revealed degenerated cells in the nuclei of the injured nerves, thus affording an opportunity of localising the anatomical position of these nuclei in man; but degenerated cells were found also in an unusual situation, the significance of which was at first uncertain. As further discussion will show, I venture to believe that these represent a system of cells analogous to those described in dogs as the nucleus salivatorious. For the following clinical notes of the case I am indebted to Dr. Rollmann, of Essen.

The patient, a miner, received a severe injury in the upper part of the neck on April 18, 1913. When a careful examination was made a few days later, the following conditions were observed:—

(1) Paralysis of the left side of the tongue.

(2) Paralysis of the left sterno-mastoid and upper part of the left trapezius.

(3) Loss of taste in the whole of the back of the tongue, more marked, however, on the left side.

(4) Paralysis of the left side of the palate. No anæsthesia of the palate could be detected.

(5) Aphonic speech.

By laryngoscopic examination the left vocal cord was seen to be immobile.

(6) Loss of power of swallowing, even for liquids.

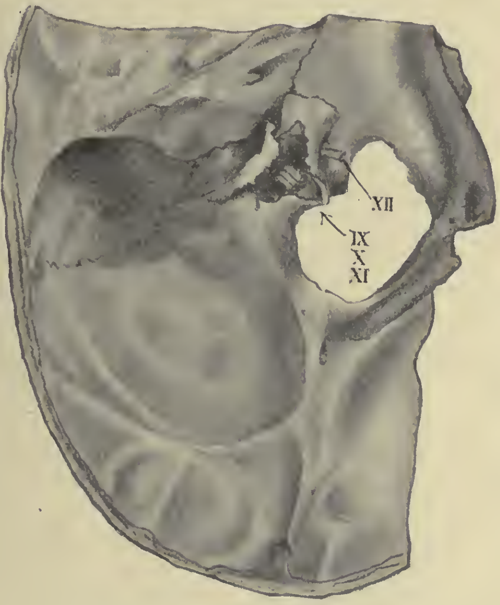
In addition to the above symptoms a slight left facial paralysis was observed on the first day after the accident, but this rapidly disappeared. It is also stated that immediately after the accident some question arose as to whether the phrenic nerve was injured or not, but on the following day no paralysis of the diaphragm could be detected. At no time was there any paralysis of the extremities, nor with the exception of the paralysis of the left sterno-mastoid and trapezius muscles was there any limitation of the movements of the neck.

In spite of careful X-ray examination no definite evidence of any fracture was discovered. The fluid obtained by lumbar puncture contained a little blood. A diagnosis of injury to the peripheral roots of the ninth, tenth, eleventh, and twelfth cranial nerves was made. Later observations confirmed those already made; the paralysis of swallowing remained absolute, marked atrophy of the left side of the tongue, and of the left sterno-mastoid and the upper part of the left trapezius followed, the sense of taste was preserved in the right anterior third of the tongue only.

The patient developed bronchitis and broncho-pneumonia, and died on June 28, seventy-one days after the accident.

At the autopsy a fracture of the posterior fossa of the skull was found, involving the jugular foramen. The injured part of the skull was sent for examination together with the brain and spinal cord. An examination of the region of the fracture discloses the following points:—

On the left side the bony ring surrounding the foramen magnum has been fractured in its middle part, in such a way that the circumference of the foramen has been rendered quite irregular. In the situation of the fracture lie splinters of bone and yellowish red masses of granulation tissue; it is evident that much callus has been thrown out. The anterior condyloid foramen, through which passes the hypoglossal nerve, lies below and in front of the fracture. The fracture has in its lateral part affected the jugular foramen, so that the nerves passing through it are directly involved in the fracture. The brain and spinal cord had been previously hardened in formalin. When examined later the brain appeared normal in general appearance and configuration; no meningitis was present, no naked eye hæmorrhages were visible. The vessels appeared natural. On the left tonsillar lobe of the cerebellum was a small area, about 2 c.cm. long by 1 c.cm. broad, where some destruction of tissue had taken place; this was evidently a result of direct pressure from callus or broken spicules of bone. The portions of the cranial nerves remaining attached to the brain showed no visible change. Sections through the brain showed no naked eye lesions.



Sketch to show position of fracture.

The cervical part of the spinal cord, the medulla, and the pons were taken, sections cut and stained by Nissl's method, in order to discover the presence of any degenerated cells in the nuclei of the injured nerves. Sections were also stained for the presence of fatty change with Scharlach red and hæmatoxylin. The material had remained in formalin too long to enable Marchi's method to be used with advantage.

Nissl's method, however, yielded interesting results; evident degenerative changes in the cells could be traced, and in this way the anatomical position of the nuclei concerned could be determined. A glance at the appended diagrams will indicate at once the anatomical position of the degenerated cells. It must be understood that the way in which the cells are depicted, viz., △ for a normal cell and ▲ for a degenerated cell, is purely a convention and bears no relation to the actual size or shape of the cells concerned. This method has only been adopted to make the position of the nuclei concerned easily seen; with the same object the diagrams are made as simple as possible.

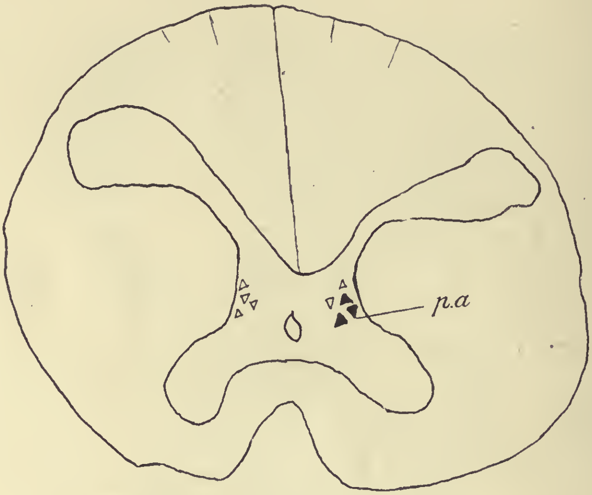


FIG. 1.—*N.a.*, nucleus accessorius.

There is nothing peculiar to record as far as the degeneration itself is concerned. As a rule the number of cells in the affected nucleus seemed reduced; the cells themselves showed the following changes: loss of a clear cell outline; displacement of the nucleus to the periphery of the cell; loss of the typical Nissl granules, with a more diffuse blue coloration of the whole cell substance, and finally, the appearance of numerous parasite glia-cells in and around the degenerated cells.

In the upper part of the cervical cord (see fig. 1) a group of degenerated cells was found lying in the ventro-lateral part of the grey matter of the left side; these cells were quite distinct from the cells in the ventral horn, which, on the contrary, were well preserved on both sides. They were considered to be cells of origin for the spinal part of the spinal accessory nerve, the degeneration being due to the injury inflicted on the trunk of the nerve in the jugular foramen.

Fig. 2 depicts the appearances observed in a section through the lower part of the medulla, at the level of the decussation of the pyramids. At this level degenerated cells are observed in three groups of cells. One was situated in the grey matter of the left side, dorso-lateral to the central canal, between the central canal and the nucleus cuneatus; only a portion of the cells of this nucleus were degenerated. These cells were regarded as belonging to the dorsal nucleus of the vagus. In the lateral nucleus, the grey matter ventral and internal to the substantia gelatinosa Rolandi, a situation corresponding to the ventro-lateral region of the grey matter of the cord, a second group of degenerated cells were visible. These cells are in all probability those of the lower part of the nucleus ambiguus, the ventral motor nucleus of the vagus group of nerves. Internal to these cells was a third and

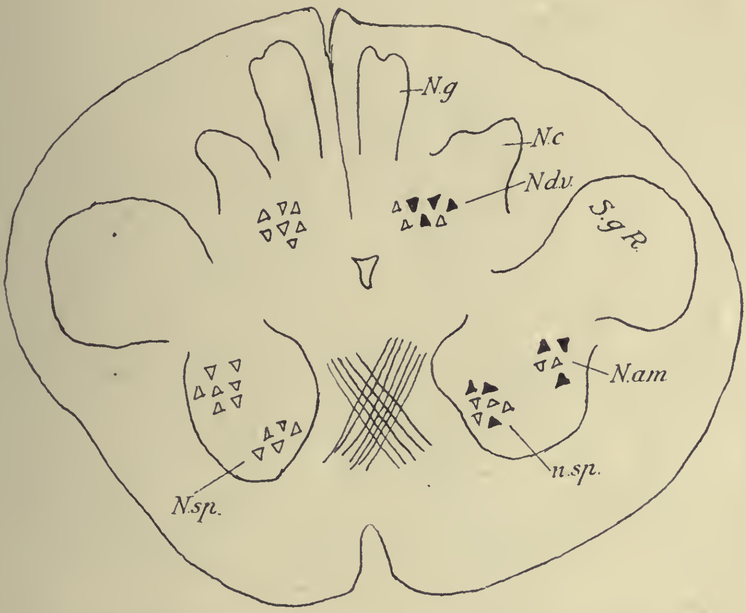


FIG. 2.—*N.g.*, nucleus gracilis; *N.c.*, nucleus cuneatus; *N.d.v.*, dorsal nucleus of vagus; *S.g.R.*, substantia gelatinosa Rolandi; *N.am.*, nucleus ambiguus; *N.sp.*, nucleus supra-spinalis.

smaller group of cells, showing similar evidence of degeneration; this group is probably identical with that described as the "nucleus supraspinalis" (Jacobsohn [1]), which is stated to lie in proximity to the nucleus of the spinal accessory nerve below, while higher up it comes into relation with the nucleus of the hypoglossal. As the nucleus of the hypoglossal is not visible in the sections under discussion, it seems reasonable to conclude that these cells have given origin to fibres which join the roots of the spinal accessory nerve.

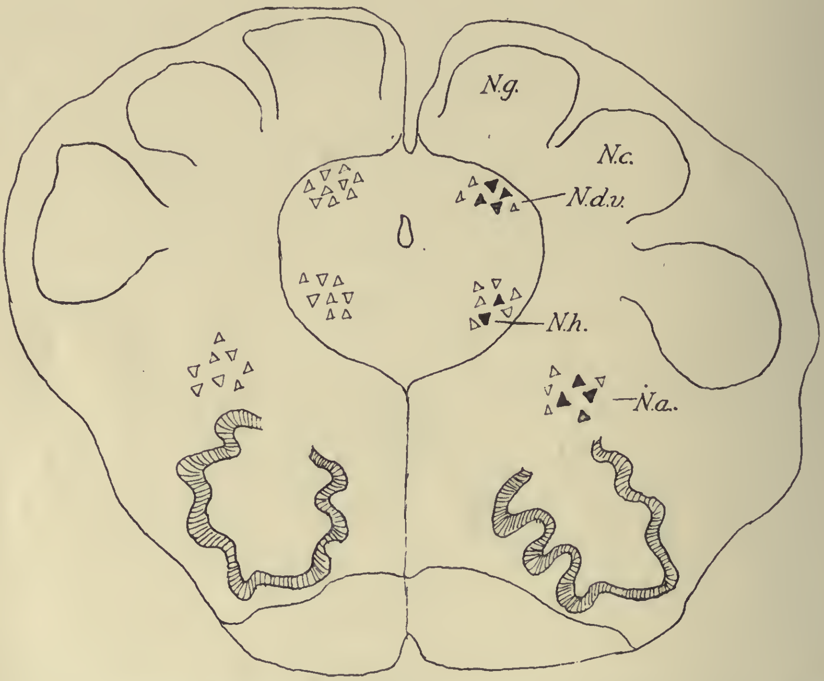


FIG. 3.—*N.g.*, nucleus gracilis; *N.c.*, nucleus cuneatus; *N.d.v.*, dorsal nucleus of vagus; *N.h.*, hypoglossal nucleus; *N.a.*, nucleus ambiguus.

Fig. 3 represents a section through the medulla oblongata at a higher level, where the inferior olives have just become developed. Here again degenerated cells are visible in three groups of cells. In the grey matter round the central canal, and lying dorso-laterally to it, degeneration is again visible in the dorsal nucleus of the vagus. The nucleus of the hypoglossal now comes into view, lying in the grey matter ventro-lateral to the central canal; many of its cells are degenerated. At this level degeneration again appears in the nucleus

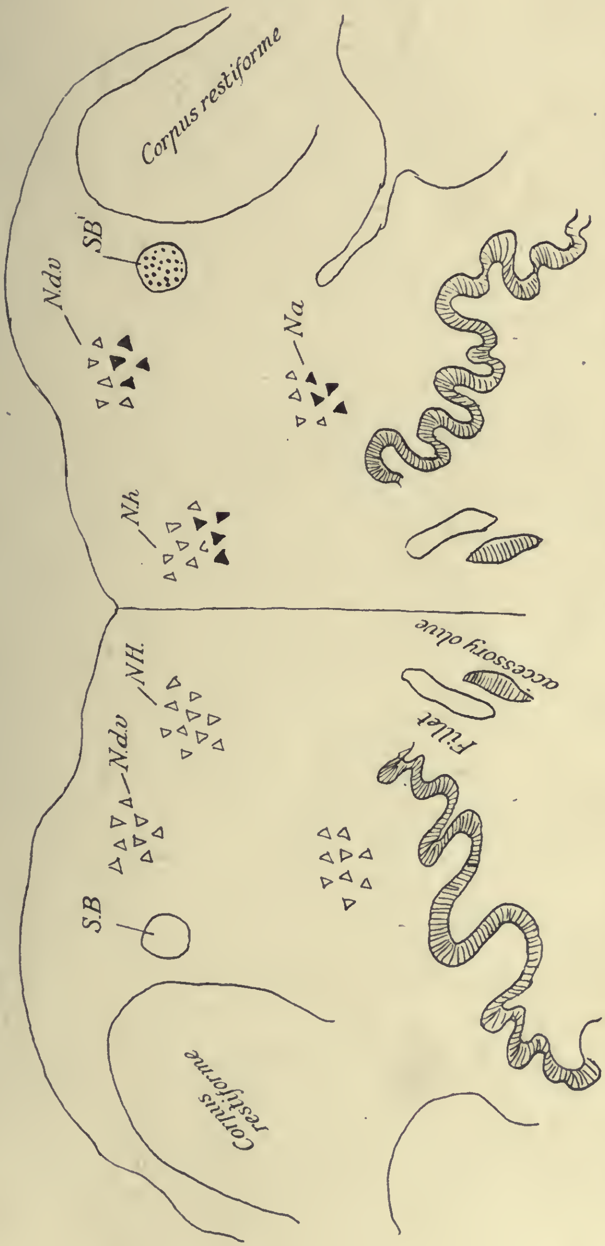


Fig. 4.—*S.B.*, solitary bundle; *N.d.v.*, dorsal nucleus of vagus; *N.h.*, hypoglossal nucleus; *N.a.*, nucleus ambiguus.

ambiguus, which lies in the grey matter ventrally and laterally to the central canal and the hypoglossal nucleus, and just dorsal to the inferior olive.

It will therefore be seen that sections through the lower and middle part of the medulla exhibited a fairly constant picture of localized cell degeneration.

Fig. 4 depicts a section through the upper part of the medulla, cutting through the restiform body at the level of the entrance of the cochlear nerve. Degenerated cells can be seen in the same groups of cells. Owing to the central canal having opened out into the fourth ventricle, the hypoglossal nucleus is placed more dorsally in the grey matter in the floor of the fourth ventricle; here degenerated cells are found in the ventral part of the nucleus only. Lying more laterally and dorsally is the dorsal nucleus of the vagus, of which some cells are degenerated. Just external to this again is the solitary bundle, which in sections stained with Scharlach red shows most striking fatty change. Except for a few scattered points fatty changes were not found elsewhere. The nucleus ambiguus is still visible, and contains degenerated cells.

Fig. 5 is a section at the uppermost part of the medulla. At this level the nucleus of the hypoglossal, the dorsal nucleus of the vagus, and the nucleus ambiguus have disappeared, but some scattered degenerated cells are visible on both sides. They lie in the grey matter just dorsal to the inferior olive, internal and slightly ventral to the facial nucleus. Fig. 6 shows a more detailed view of these cells. The exact significance of this degeneration would be a little uncertain if the experimental researches of Kohnstamm and Wolfstein [4] and Yagita and Hayama [6] had not thrown some light on the question. Kohnstamm [2, 3] has described in dogs a system of large cells which showed Nissl degeneration after cutting the lingual nerve and nerve to the submaxillary gland; this system of cells, which he calls the "nucleus salivatorius superior," lies at the junction of the medulla with the pons, just dorsally to the facial nucleus. The cells extended from the caudal end of the facial nucleus to the frontal end of the trigeminal nucleus; some of the cells were scattered over a wide area, reaching the raphe mesially, Deiters' nucleus laterally, and the floor of the fourth ventricle dorsally. After a unilateral lesion degenerated cells were found on both sides. It has further been observed that affection of the parotid secretion follows cutting of the glosso-pharyngeal nerve, and Kohnstamm described a caudal prolongation of the nucleus salivatorius, fibres from which pass out with the glosso-pharyngeal nerve; the cells of origin of these fibres lay in the ventral part of the medulla between the inferior olive and the nucleus ambiguus, beginning above at the caudal end of the facial nucleus. To this latter group of cells Kohnstamm gave the name "nucleus salivatorius inferior," and considered that the two together form a centre for the innervation of the salivary glands. By Marchi's method he was able to trace fibres from the nucleus as far as the submaxillary ganglion.

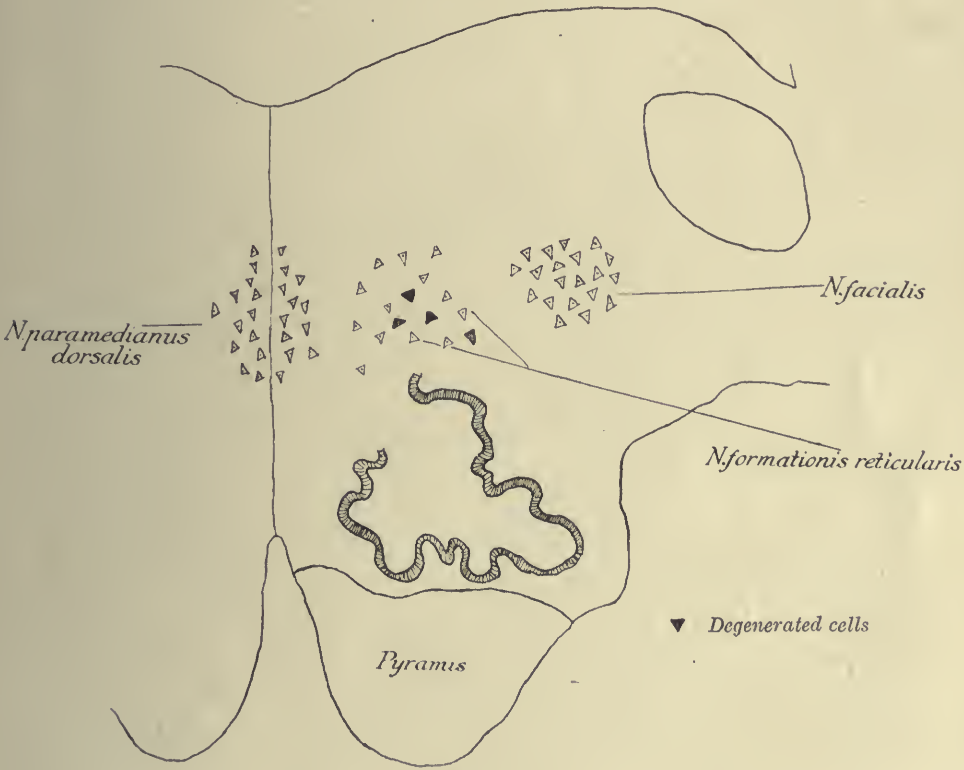


FIG. 5.

Yagita and Hayama [6] cut the tympanic branch of the glosso-pharyngeal nerve in dogs and found degeneration in the situation of Kohnstamm's inferior nucleus. Scattered degenerated cells were also found in the grey matter of the formatio reticularis of this region, in a situation slightly more ventral and mesial than the nucleus already described.

Yagita [5] considered that the secretory centre of the parotid is a direct caudal prolongation of the nucleus salvatorius lying in the formatio reticularis at the level of the most caudal part of the facial nucleus. The position of the degenerated cells found in my sections corresponds to the scattered degeneration described by Kohnstamm and Yagita. In my sections they are seen to extend from about the level of the entry of the cochlear nerve below to the termination of the inferior olive above; they are not, however, present in every section, and cannot be said to constitute a definite nucleus. In view of the experimental observations quoted, I would suggest that these cells represent cells of origin for the secretory fibres which pass out with the glosso-pharyngeal nerve, and which subsequently, by means of its tympanic branch, become distributed to the parotid gland. Unfortunately no clinical evidence was forthcoming as to the presence of any disturbance of salivary secretion; owing to the paralysis of swallowing, the saliva simply dribbled from the mouth, and the explanation of the degenerated cells found is based upon the similar appearances found in dogs. Further observations may perhaps confirm the existence of a salivary centre in the human medulla.

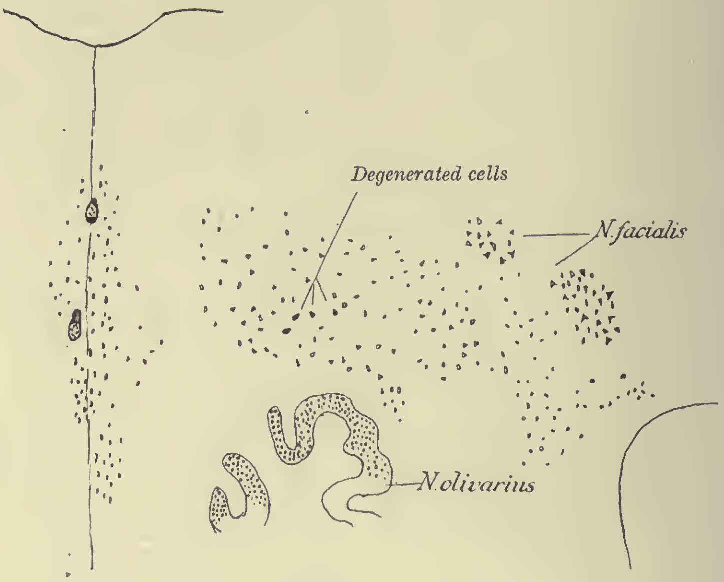


Fig. 6.

The anatomical changes found may be summarized as follows:—

(1) Degeneration in the cells of origin of the spinal accessory nerve

in the ventro-lateral part of the grey matter of the upper cervical region of the spinal cord.

(2) Degeneration throughout the whole length of the nucleus ambiguus.

(3) Partial degeneration of the dorsal nucleus of the vagus.

(4) Partial degeneration of the hypoglossal nucleus.

(5) Marked fatty change in the solitary bundle.

(6) Scattered degenerated cells in the grey matter of the upper part of the medulla, just dorsal to the inferior olive.

It was somewhat surprising to find such a small amount of fatty change present, it being practically confined to the solitary bundle. The long time elapsing between the injury and the death of the patient (over two months) is no doubt in part a reason for the limited amount of fatty change present. Since the dorsal nucleus of the vagus, which is largely a sensory nucleus, showed only partial degeneration, we may surmise that perhaps the injury to the nerve took place on the distal side of the ganglion, the degenerated cells representing the motor part of this nucleus. In this case the fatty change in the solitary bundle would represent degenerated fibres from the glossopharyngeal nerve. It was, however, impossible to say at exactly what point in their course through the jugular foramen the nerves were injured.

From the fact, too, that the hypoglossal nucleus showed only partial degeneration, we may assume that the injury to the nerve was not complete, a hypothesis which is borne out by an examination of the skull, for, as will be seen from a reference to the sketch, the fracture did not directly involve the anterior condyloid foramen.

In conclusion, I would like to express my gratitude to Professor Edinger, who not only placed the material at my disposal for examination, but also afforded me invaluable assistance in the interpretation of the anatomical changes found.

REFERENCES.

[1] Jacobsohn. "Über die Kerne des menschlichen Hirnstamms," *Neurol. Centralbl.*, 1909, Bd. xxviii, S. 674.

[2] Kohnstamm. *Anat. Anzeig.*, 1902, Bd. xxi, S. 362.

[3] *Idem.* "Vom Centrum der Speichelsekretion, etc.," *Verhandl. des XX Cong. f. inn. Med.*, 1902, S. 361.

[4] Kohnstamm und Wolfstein. "Versuch einer physiolog. Anatomie der Vagusursprünge und des Kopfsympathcticus," *Journ. für Psychol. u. Neurol.*, 1907, Bd. viii, S. 177.

[5] Yagita. "Weitere Untersuchungen über die Speichelsekretion," *Anat. Anzeig.*, 1909, Bd. xxxv, S. 70.

[6] Yagita und Hayama. "Über das Speichelsekretioncentrum," *Neurol. Centralbl.*, 1909, Bd. xxviii, S. 738.

PUBLICATIONS RECENTLY RECEIVED.

[*Notes on a book under this heading do not preclude a subsequent review.*]

Behandlung der angeborenen und erworbenen Gehirnkrankheiten mit Hilfe des Balkenstiches. Von Professor G. ANTON und Professor F. G. von BRAMANN. S. 188, mit 44 Abbildungen und 10 Tafeln. Berlin: Karger, 1913.

The authors recount five years' experience of the operation of "Balkenstich," on a large number of cases. As the free communication between the ventricles and the subdural spaces of the brain and cord, which is necessary for the proper circulation and nutrition of the brain, is often blocked, they have attempted to make an artificial communication through the corpus callosum. Through a small opening 1½ to 2 cm. behind the coronal suture and the same distance from the middle line, a blunt round-ended cannula with lateral openings is introduced between the hemispheres and passed along the falx cerebri, through the corpus callosum into the anterior horn of the lateral ventricle. When the ventricle has been drained to the extent required, the opening into it is enlarged, and then, according to the authors, generally remains patent.

The effects of this operation in a large number of cases of hydrocephalus, cerebral tumours, hypophyseal tumours, epilepsy, &c., are fully described. No death or serious accident could be attributed to the operation in any of the fifty-three cases on which the authors performed it, and in all in whom the intracranial tension was increased, considerable relief was obtained.

Contribution à l'Étude anatomo-clinique des Monoplegies d'Origine corticale. Par le Dr. M. REGNARD. Pp. 216, with 12 plates. Paris: Vigot Frères, 1913.

This monograph is based on the examination of ten cases, supplemented by a diligent compilation of similar cases published by others; but unhappily these observations were not always abstracted from the original descriptions.

The methods of examination employed, especially in the investigation of sensation, appear to have been relatively complete, but the conclusions add little to our knowledge. The author concludes that the motor centres lie entirely in the precentral and paracentral convolutions, and the individual centres are segmentally arranged within them. The sensory zone occupies the precentral gyrus, but also extends behind the fissure of Rolando and over part of the parietal lobe. This sensory zone is divided, as is the motor area, into centres corresponding to the different segments of the body, each of which lies at the same horizontal level as, and contiguous to, the corresponding motor centre.

Map-Scheme of the Sensory Distribution of the Fifth Nerve (Trigeminus) with its Ganglia and Connexions. By L. HEMINGTON PEGLER. London: Ballière, Tindall and Cox, 1913.

This is a most successful attempt to represent in a comprehensive though simple manner the relations and distribution of the various branches of the trigeminal nerve, and their connexions and anastomoses with other cranial nerves, and especially with the cervical sympathetic fibres.

In many instances simplified or modern titles have replaced older morphological terms, but the main object of the map is to illustrate the functional relationships of the various branches of the nerve, which must be considered in dealing with the etiology of the neuralgias, headaches and referred pains which so frequently result from irritation of its fibres. It is with this end in view too that insets are attached to the map, the one showing the central (bulbo-pontine) relations of trigeminal fibres to other afferent centres, and consequently the possible distribution of pain referred from them; the other, the relation of the peripheral distribution of the fibres of the three trigeminal divisions to that of the cervical roots.

The functional significance of the ganglia and fibres that make up the peripheral branches of the trigeminal nerve are indicated concisely but clearly on the map, and are dealt with more fully in the analytical tables of the anatomy and physiology of the nerve, and of its ganglia and connexions that are supplied with it.

The map, which measures 49 by 59 in., has evidently been designed with extraordinary care and accuracy, and incorporates the latest and most trustworthy knowledge on its subject. It will be found extremely valuable to anatomists in teaching the complicated relations of this nerve, and especially to clinicians in elucidating and studying the seat and extent of the referred headaches and pains so commonly due to affection of its fibres in the skull, face, mouth, nose or ears.

Arbeiten aus dem Pathologischen Institut der Universität Helsingfors, herausgegeben von Professor E. A. HOMÉN. Neue Folge, 1ter Band, 1tes und 2tes Heft. Jena: Fischer, 1913.

These parts of the first volume of a new series edited by Homén contain a number of valuable papers, chiefly on the pathology and pathological anatomy of the nervous system.

Homén himself contributes an elaborate paper on the origin and development of cerebral abscesses, and the nature of the cells that are found in and around them; Wallgren writes on the finer histological changes in poliomyelitis and insists on its inflammatory nature and the important part the glia-cells play in it; Fabritius has an interesting clinical and pathological paper on acute myelitis and spontaneous hæmatomyelia, and also describes the histological features of a case of sclerotic atrophy of one hemisphere of the brain; and Silfvast deals with the clinical and pathological characters of tumours at the base of the brain in the region of the hypophysis.

Handbuch der Nervenkrankheiten im Kindesalter. Von Professor L. Bruns, Professor A. Cramer, Professor Th. Ziehen. S. 980, mit 189 Abbildungen im Text und 3 Tafeln. Berlin: Karger, 1912.

The three authorities on nervous disease have described in this work all those affections of the nervous system which can occur in children. The sections vary greatly in completeness, some form short, admirably written monographs, others follow more the style of a text-book. This handbook will be of value to all who are interested in the diseases of childhood. It is profusely illustrated.

Leitfaden der Elektrodiagnostik und Elektrotherapie für Praktiker und Studierende. Von Dr. Toby Cohn. Vierte vollständig umgearbeitete und vermehrte Auflage. S. 212, mit 6 Tafeln und 65 Abbildungen. Berlin: Karger, 1912.

This excellent little handbook has passed into a fourth edition, but though there are many additions, it retains its previous form. It forms a complete guide to the use of electricity in diagnosis and treatment.

Freud's Theories of the Neuroses. By Dr. Eduard Hitschmann (Vienna). Translated by Dr. C. R. Payne. Nervous and Mental Disease Monograph Series, No. 17. Pp. 154. New York: Journal of Nervous and Mental Diseases Publishing Company, 1913.

In this book the author gives a systematic exposition of the views of Professor Freud, who has revised the work throughout. Each chapter is devoted to one aspect of his psychology, especially in relation to functional nervous disorders. In many cases direct quotations are made from Freud's writing, but the whole gains a coherence which is of necessity absent from the originals. The translation is remarkably good, especially in view of the extreme difficulty of the German, and the complexity of the new terms introduced by Freud.

Ueber Nervöse Entartung. Von Professor Dr. OSWALD BUMKE. S. 120. Berlin: Springer, 1912.

Kraepelin defines degeneration as the appearance of inherited qualities, which make it either difficult or impossible for the creature to attain the general aims of life. In mental medicine degeneration signifies a steadily increasing deterioration of the state of nervous health. These complicated questions are dealt with in this work from consideration of our present day knowledge, without special research or investigation of records, and the author concludes that Germany at any rate is not decadent. The general prevalence of functional nervous disorders is simply the result of the social conditions.

Acute Poliomyelitis. By Dr. IVAN WICKMAN (Stockholm), translated by Dr. J. W. J. A. M. MALONEY. Pp. 135. New York: Journal of Nervous and Mental Diseases Publishing Company, 1913.

This is an excellent translation of Wickman's work noticed in BRAIN, vol. xxxv, p. 191. It is far the best summary account we possess of our knowledge of this disease. The plates are admirably reproduced.

Die Gesche Gottfried, eine Kriminalpsychologische Studie. Von Dr. L. SCHOLZ. S. 160, mit 6 Abbildungen. Berlin: Karger, 1913.

The heroine of this extraordinary story was born in 1785 in Bremen, and was executed in 1831, after having poisoned innumerable persons with arsenic. Among her victims were her parents, both her husbands, her children, her devoted servant and several of her most intimate friends. On one occasion she started for a visit provided with rat-paste. She was universally beloved, especially on account of the wonderful devotion she showed in nursing her victims. Her ambition was in every case to kill extremely slowly in order that she might have the pleasure of attending the sick. Documents and portraits are given, and this pamphlet should be in the hands of all who are interested in this remarkable group of criminals.

Dreams and Myths. By Dr. KARL ABRAHAM (Berlin). Translated by WILLIAM A. WHITE, M.D. Nervous and Mental Disease Monograph Series, No. 15. Pp. 74. New York: Journal of Nervous and Mental Diseases Publishing Company, 1913.

Freud in a remarkable study analysed the Œdipus story in the light of his psychological views. This book is an attempt to carry such analysis further to explain the Prometheus myth and the stories of Moses, Samson, and other folk-heroes. The time is, however, scarcely ripe for so wide an extension into so uncertain a branch of anthropological knowledge. The translation is well carried out.

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Members of the Neurological Section of the Royal Society of Medicine can obtain the Index of "Brain" for the Volumes I. to XXIII. inclusive, that is, from its commencement to the end of 1900, from Messrs. MACMILLAN & CO., Ltd., St. Martin's Street, London, W.C., at the price of 6s. 6d., post free.

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EDITOR.

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BRAIN.

PARTS III. & IV., VOL. 36.

LYMPHOGENOUS INFECTION OF THE CENTRAL NERVOUS SYSTEM.

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THE obscurity which surrounds the genesis of almost all inflammatory lesions in the central nervous system, and of those which are degenerative except where a focal lesion exists, will be admitted. The questions of the causation of the lesion, the point of origin of the morbid change and its propagation, are constantly recurring in regard to cases of meningitis, myelitis, tabes dorsalis, dementia paralytica, and the non-systemic scleroses, and the theories advanced have often been based on assumptions devoid of proof which have tended rather to divert the investigator from, than to lead him on to, the right path. Nor should one be astonished that this is so, for the intricate anatomy of the nervous system, its complexity of function, and its comparative inaccessibility to experimental methods, have taxed the ingenuity of the investigator to the utmost. Hence the theories regarding the genesis of many morbid phenomena have been based upon deductions built up on the examination of tissue in which the chronicity of the changes obscured the original starting-point of the retrograde or inflammatory process. This applies particularly to subacute and chronic lesions, systemic and non-systemic, affecting the columns of the spinal cord.

For years it has been apparent that continued examination of these chronic lesions while increasing our knowledge in detail yet failed to widen it in regard to etiology, and though toxic influence naturally received due recognition, its source and mechanism of action remained unexplained. It seemed obvious, therefore, that investigation ought to be directed towards elucidating the mechanism of production of those lesions and the first step naturally involved a study of all possible paths of infection and intoxication. It is with one of these, infection via the lymphatic system of peripheral nerves, that this paper mainly deals; and in it we propose to give a synopsis of our observations in clinical cases and experiment. Much of the detail on which our conclusions have been founded must necessarily be omitted; that will be found in the appended list of publications.

In all probability the controversy surrounding the genesis of the lesion in tabes dorsalis and the recognition of dementia paralytica as an inflammatory disease were most important factors in directing attention to the lymphatic system of the cerebrospinal axis; and an important step forwards was taken with the demonstration of a continuity of the lymph-stream in peripheral nerves with that of the spinal cord. The injection into nerves of organisms and coloured substances showed that the lymph-stream was an ascending one towards the cord and that the main current lay at the periphery of the nerve-bundles immediately under the fibrous sheath. It must be borne in mind, however, that this statement regarding the main current of lymph in nerves was based on experiments in which organisms have been injected into the nerve substance. Where infection occurs from without it will be shown that diffusion of organisms and toxins can take place along the outer surface of nerves and give rise to an ascending epi- and perineuritis.

Infection along peripheral nerves had been deduced for many years in regard to tetanus and rabies, and the recognition of a wider application of this principle suggested a new line of research along which an explanation of certain other pathological phenomena might be sought. Valid proof of the principle will be found in the following short résumé of the literature.

Marie and Morax [18] cut the nerve to the fore limb of an animal, and later injected a lethal dose of tetanus toxin into its paw with a negative result. Homén and Laitinen [13] injecting streptococci into the sciatic nerve, traced them upwards into the meninges of the cord; while Pirrone [34], employing the pneumococcus, found changes in the cord limited to the side corresponding to the infected nerve. In addition to organisms, chemical and inert substances yielded equally instructive results. Guillain [12] injected ferric chloride into the sciatic nerve, and subsequently introducing potassium ferrocyanide into the general circulation found Prussian blue in the posterior roots; he also found that coloured fluids diffused from the pial lymph spaces of the posterior part of the cord into those of the posterior columns. Marie and Guillain [19] concluded from their work that there is a common lymph system for the posterior roots, the posterior columns and the pia covering them, and that the lymph flows freely in the intervals between the fibres and other structures. They state that tabes is a lesion of this system, most probably of syphilitic origin. Sicard and Bauer [39] injected china ink into nerves and found that the granules ascended along them to the cord; and according to D'Abundo [2] and Guillain [12] the lymph in the posterior columns pursues an ascending course and simultaneously passes forwards towards the central canal. In these experiments therefore we are afforded ample evidence of the possibility of lymphogenous infection of the central nervous system.

Homén's [13] investigations are particularly convincing. Twenty-four hours after the injection of bacteria into the sciatic nerve, they accumulate in the lymphatic space situated on the internal surface of the perineurium and can be traced along the internal surface of the capsule of the spinal ganglion, along the inner surface of the perineurium of the spinal roots, especially the posterior, and into the cord meninges, from which they spread into the peripheral zone of the cord and especially along the postero-median septum. The bacterial invasion is accompanied by inflammatory reaction, which on experimenting with pure toxin is of less degree and inconstant.

Spitzer's [40] experiments, too, are extremely interesting. He injected an infusion of jequirity (*Abrus præcatorius*) into the dental pulp of a dog and killed it after some days. Microscopic examination revealed an ascending inflammatory neuritis spreading up to and implicating the Gasserian ganglion. Zalla [44], in whose monograph there is an excellent review of the observations on ascending neuritis, has employed the same methods of experiment as Spitzer [40] and Homén [13]. He has not confirmed the former's work but acknowledges the great importance of Homén and Laitinen's [13] researches. Zalla [44], employing the *Bacillus pyocyaneus*, demonstrated acute inflammatory phenomena, spreading up the sciatic nerve through the spinal ganglia and spinal roots, especially the posterior, into the cord and meninges. After careful criticism he agrees that Homén's [13] conclusions are correct and admits the possibility of the diffusion of an inflammatory process along peripheral nerves to the central nervous system by experiment. While admitting this experimental diffusion he is careful at the same time to point out that it differs greatly, in its course, from the true ascending neuritis found in the human subject. This point, however, need not be considered at the present moment; it is of minor importance as compared with the fact that organisms and toxins can reach the central nervous system by diffusion along the lymph path of peripheral nerves.

EVIDENCE OF INFECTION OF THE CENTRAL NERVOUS SYSTEM BY TOXIC DIFFUSION ALONG THE PERINEURAL LYMPH SYSTEM IN CLINICAL CASES (LYMPHOGENOUS INFECTION).

In 1903 we had the opportunity of examining the nerve tissues in a case of left brachial neuritis of twelve days' duration. The exciting agent in this instance was the *Staphylococcus pyogenes aureus.* We found the brachial plexus bathed in pus which had burrowed among the cervical muscles as well and surrounded the root ganglia of the cervical cord. The microscopic examination of the tissues proved of great interest. The loose areolar tissue round the spinal root ganglia of the left side was greatly inflamed, the veins were thrombosed and contained many cocci. Those not thrombosed were greatly congested; the arterioles, on the other hand, showed no morbid change. In the ganglion capsule there were hæmorrhages and cocci, more evident in the outer layers, and amongst the nerve-cells dilated venules and capillaries containing micro-organisms. Similar changes affected the perineurium of the brachial plexus, but to a less degree. No cocci were found in the dura of the cervical cord or loose areolar tissue covering it. One small group only was observed in the pia-arachnoid covering the posterior columns. There were no inflammatory phenomena in either membrane. The 6th and 8th cervical root ganglia of the right side were examined. There were no thrombi in the capsular areolar tissue, but scattered hæmorrhages in which were a few cocci. No cocci were found in the ganglion substance.

The extramedullary portion of the anterior and posterior cervical roots was examined for degeneration by Marchi's method and none was found. In the spinal cord, however, the same method demonstrated an acute degeneration whose distribution was confined to the cervical region. The seventh, sixth, and fifth segments showed much the greatest degree of degeneration. There was marked degeneration of the intramedullary portion of the left posterior root, which, commencing at the point where the fibres lose their neurilemma sheath, affected the middle area of the root entry zone. On the right side the degeneration affected the same area, but was less marked. There were degenerated fibres on each side of the postero-median septum. In the lateral columns of the cord on either side of the septa derived from the pia-arachnoid there was a considerable degree of myelin degeneration; and here and there in the posterior and lateral regions there were degenerated myelin droplets at the cord margin. A considerable degree of degeneration was observed in connection with the intramedullary portion of the anterior roots in their whole course from the cord periphery to the grey matter. There was degeneration of the collaterals running from the left root entry zone to the anterior cornual cells, and also of the anterior commissure. All the vessels of the cord and meninges were greatly congested.

Special attention should be directed to one point in this case, and that is the presence of a gross degenerative lesion in the spinal cord of purely toxic origin. The toxins must have passed along the perineural lymphatics from the infective area round the spinal ganglia and brachial plexus; once having gained the cord they flowed with the lymph into the anterior and posterior root entry zones, and also round the cord in the meshes of the pia. When we come later to study the inflammatory lesions induced by infecting the lymphatic system of nerves it will be seen that precisely the same situations are involved.

Further evidence will now be brought forward in the following series of cases in support of the view that lesions of the spinal cord can result from the diffusion of toxins upwards along nerves from peripheral foci of infection. The description of the cases is condensed in order to save useless repetition.

Case 1.—Bedsores: gluteal region, more severe on left side; suppuration of right elbow.	Degeneration of the posterior columns and of the anterior radicular fibres in the lumbo-sacral region from S1—L3, more intense on the left side and in L4. From D12—D2 there was nothing worthy of note. Degeneration again commenced at D1 in the root entry zone of the right side; the lesion was most marked in C7 and C6, and gradually diminished in the next few segments.
Case 2.—Bedsores on buttocks and sacrum: of longer duration on the right side.	Lesion most intense on the right side. Slight degeneration of posterior columns in S1; maximum in L4 and 3: diminished gradually in the segments above this level.

Case 3.—Pelvic cellulitis, renal abscesses, double empyema of longer duration on the left side, abscesses in the cervical muscles.	Very slight degeneration of the posterior columns in the sacral region. Much Marchi reaction among the anterior radicular fibres of S4—3—2, especially on the left side. No changes in the lumbar cord. Degeneration in the root entry zones of D11—10—9; again a separate lesion beginning in the root entry zone of D5, more marked on the left side, and occurring in every segment as high as C4. In the cervical region the degeneration was greatest in C7 and 6.
Case 4.—Caries of the 4th and 5th lumbar vertebræ; psoas abscess on the right side, which became septic two months before death.	In S2 a slight lesion of the posterior columns, which increased in S1, and was most intense is L4 and 5. Above this level it gradually diminished. The lesion was much more marked on the right side.
Case 5.—Chronic suppuration of right knee-joint.	Degeneration of the posterior columns from S1 to the lower dorsal region, most marked on the right side and in L4—3—2.
Case 6.—Chronic suppuration of left knee-joint.	Lesion of the posterior columns most intense on the left side; slight in S1, well marked in L5—4—3. The lesion ceased at D11.
Case 7.—Prostatic cancer; chronic cystitis.	Followed by transverse myelitis at level of D8 and 9.

All the above cases were studied by the Marchi method for myelin degeneration, and all showed involvement of the posterior columns in that region of the cord which corresponded to the nerve supply of the infective focus. At times also the anterior radicular fibres were affected. Case 1 and the case of brachial neuritis illustrate these two points very well. Another noteworthy point is that the degeneration of both anterior and posterior spinal roots always begins at the point where the fibres entering the cord lose their neurilemma sheath, that is in the intramedullary portion, and in the case of the anterior roots the degeneration in some instances has been traced from the cord margin into the grey matter, where it terminated among the cells. The effect of the toxins is not always exerted on the lateral portions of the cord. In the case of brachial neuritis, however, we find the lateral diffusion very marked, a fact to be explained in all probability by the high activity of the infective focus and its close proximity to the spinal cord. The greater the degree of toxicity, therefore, in the lymph-stream, the more diffuse the cord lesion.

The extramedullary portions of the spinal roots in the above cases were examined for degeneration with a negative result. It seems clear, therefore, that toxins can ascend along the perineural lymphatics without producing parenchymatous changes in the nerves. On reaching the cord, however, they give rise to a degeneration of the myelin sheaths with which they come into contact. At the same time, in saying this we do not mean to affirm that parenchymatous changes are absent in all cases. It will be shown in another part of this paper how organisms and toxins cause an epi- and perineuritis as they pass upwards along the nerves; and it is conceivable that such, if of an acute nature or in action for a prolonged period, would tend to induce secondary parenchymatous changes, especially were an extension of the inflammatory process to take place along the septa between the nerve-bundles.

EVIDENCE OF LYMPHOGENOUS INFECTION OF THE CENTRAL NERVOUS SYSTEM FROM EXPERIMENT: DEGENERATIVE LESIONS.

When the examination of clinical material had shown that lesions in the central nervous system had a definite anatomical relationship with the nerve supply of peripheral infective areas, and that these lesions depended upon toxic diffusion along the perineural lymphatics, it seemed that to submit this view to experiment would be the most certain method of obtaining definite data.

Instead of injecting organisms or toxins into the nerves on which it was proposed to operate, we placed a celloidin capsule containing a broth culture of a micro-organism in contact with the nerve. In one series of experiments this was placed under the gluteal muscles alongside the sciatic nerve; in another series under the skin of the cheek. The animals experimented upon were rabbits and dogs, and the organisms used were *Staphylococcus pyogenes aureus*, *Bacillus pyocyaneus*, Gaertner's bacillus, *B. coli*, *B. botulinus*, and a culture of a diphtheroid bacillus obtained from a case of dementia paralytica. We commenced experimenting with all these bacilli, but later adopted a strain of *S. aureus* whose virulence had been raised. It was also found expedient to renew the capsule at intervals. Some of these capsules remained intact, others did not, and a variable amount of leakage occurred. The tissues from the first series of experiments were prepared for examination of the degenerative changes in the medullated fibres of the nerves, cord, medulla, and pons. Marchi's osmic acid method was employed. Those from the next two series were prepared to demonstrate the inflammatory phenomena. The capsules were left *in situ* for periods of from fourteen days to six weeks. Control experiments were carried out with capsules containing sterile broth.

Capsule in Contact with Sciatic Nerve.

In the lowest segments of the cord no degeneration was found. Marchi's method, however, gave a positive reaction in the lumbar enlargement. The degeneration of the exogenous system of the posterior columns was seen to begin immediately at the point where the fibres lose their neurilemma sheath; it involved the root entry zone and the remainder of the columns with the exception of a small area behind the commissure and the posterior periphery of the cord. There was considerable degeneration of the collaterals, which principally affected those running through the antero-internal angle of Rolando's substance in the posterior grey horn; those passing towards the anterior cornua showed much less alteration. The degeneration diminished rapidly in the lower dorsal segments.

In one experiment a capsule was also placed under the muscles of the upper dorsal region. The capsule ruptured and at *post-mortem* pus was found among the cervical muscles of the right side. There was degeneration of the posterior columns in the lumbar enlargement, distributed as noted above, which steadily decreased from below upwards, and in the lower dorsal cord consisted in a few scattered fibres round the postero-median septum. In the upper dorsal region considerable degeneration again appeared in the root entry zones, especially of the right side: this, however, was not so systemic in character as that of the lumbar region. In the cervical cord there was a marked increase in the number of degenerated fibres which filled the posterior columns, with the exception of the zone immediately behind the commissure and that adjoining the cord periphery. The collaterals leaving the root entry zones were degenerated, but not further anterior than the level of the commissure.

In one case there was also degeneration of the lateral columns in the vicinity of the posterior horns. The extramedullary portion of the posterior roots was examined by Marchi's method: no degeneration was present.

Capsule under Skin of Cheek.

The medulla and pons were cut in serial section and the Marchi method demonstrated degeneration of the cranial nerves in their intramedullary course. The degree of degeneration varied in intensity as well as in type.

Third nerve.—There was a high degree of degeneration of the third nerve from its point of emergence back to the nucleus of origin, towards which the morbid change diminished in intensity. The degenerated myelin showed as long, thin, black threads arranged in parallel or sinuous rows and with moniliform swellings.

Fourth nerve.—There was less degeneration in this than in the third nerve. There were short sinuous black filaments at the point of emergence. The degenerative phenomena decreased rapidly from below upwards and were absent at the nucleus of origin.

Fifth nerve.—The morbid change in both sensory and motor portions was very marked. In the latter were short, thin, black filaments with moniliform swellings intermingled with swollen globules which could be traced into the principal nucleus of origin and for a short distance upwards along the mesencephalic root. In the former there was a higher degree of degeneration which could be traced for a variable distance in the descending root; in one case the degeneration extended down as far as the lower part of the medulla. The degeneration began at the point where the neurilemma sheath ceases to exist, was very profound especially at and immediately inside this point, and all the way down the root was identical with the appearances found in Wallerian degeneration.

Sixth nerve.—There was a greater degree of alteration in this nerve than in any of the others, and the morbid appearances were similar in character to those in the third nerve. The maximum of degeneration occurred in this nerve between a point just posterior to the corpus trapezoides and the margin of the pons. Here the myelin was fused into short and long masses of somewhat sinuous outline; some ended in swollen bulbs, others were prolonged into fine black threads. There were many scattered isolated threads and also polymorphic globules. In the middle third of the nerve were sinuous rows of fine black filaments running parallel to each other, and towards the nucleus of origin these filaments of degenerated myelin were finer, fewer in number and could be traced curving round the ascending portion of the seventh nerve to the floor of the fourth ventricle.

Seventh nerve.—The degeneration here was much less. It commenced at the point where the neurilemma left the nerve-fibre and decreased centralwards; near the nucleus there were merely traces of altered myelin. In the distal portion and ascending limb the degeneration was mostly of the fragmentary type mixed with a few black filiform varieties.

Eighth nerve.—The degree of degeneration was slight and only seen in the cochlear division where there were a few black threads with moniliform swellings ending abruptly lateral to the restiform body.

Ninth, tenth, eleventh, and twelfth nerves.—In these there were no changes worthy of note. The extramedullary portion of the cranial nerves was examined by Marchi's method and no degeneration was present. The degeneration in the pons and medulla was strictly confined to the intramedullary course of the nerves, except in one instance where there was some degeneration of the fibres of the corpus trapezoides on either side of the sixth nerve for a short distance.

The alteration in the myelin sheaths is rather unusual, especially that in the motor cranial nerves. In the sixth, for example, there were many grades of degeneration. In the initial stage the myelin stained darkly (Marchi method), was swollen and vacuolated, later it formed thick fusiform masses and then elongated moniliform structures. The distal segment of the intramedullary portion of the nerve suffers most, and presumably the morbid change spreads from the periphery to the nucleus of origin. With this there is no change in the extramedullary part, so that the degeneration is clearly not Wallerian. The mode of extension and the appearance of this variety of degeneration is typical of acute toxic infection and is known as "segmentary necrosis." The black fusiform masses and long sinuous threads indicate an acute necrotic or liquefactive change in the medullary sheath.

In all the other cranial nerves and in the spinal cord one can see abundant evidence of primary myelin degeneration of varying degree. At times the sheath showed degeneration in the neighbourhood of the axis cylinder, at others the periphery was affected. In the descending root of the fifth in the pons and medulla, and in the root entry zone and collaterals of the spinal cord the degeneration was typically Wallerian in character, the degenerate myelin fragments and globules lying in rows along the course of the nerve and reaching in the case of the fifth cranial nerve to the lower part of the medulla.

From the clinical cases and the results of experiments we arrive at the following conclusions: (1) In spinal and cranial nerves there is an ascending lymph-stream to the central nervous system whose main current lies in the spaces of the perineural sheath. Toxins reach the spinal cord and brain by this route; and although they spread to some degree in the lymph-spaces of the pia-arachnoid, and so may affect structures at a distance from the point of entrance, they pass for the most part in the main stream along the nerve roots into the substance of the central nervous system. (2) Outside the central axis the nerves are possibly protected by the vital action of their neurilemma sheath; most probably, however, it is the peripheral situation of the lymph current which is the deciding factor.

The following case, of which we give an abstract, confirms many of the observations to which we have just drawn attention. It was one of general paralysis of the insane, and at the autopsy in addition to the usual morbid appearances there was acute hæmorrhagic ulceration of the colon, especially in the lower portion, and an acute cystitis. The urine was blood-stained and very offensive. There was in addition suppuration in the right knee-joint of two weeks' duration. Cultures were made of the cerebrospinal fluid in the lateral ventricle and from the lumbar region, which yielded an abundant growth of a bacillus, rod-shaped as a rule, but often long and thread-like. The right sciatic nerve was examined for organisms with negative result. They were found abundantly in the following regions, however: the internal layers of the perineural sheath of the posterior and anterior lumbar spinal roots, amongst the fibres of the posterior root entry zone, in the lymph-spaces of the pia-arachnoid round the cord margin, in its septa passing into the cord where they were most numerous at the periphery, in the intramedullary portion of the motor fibres, and in the central canal and its neighbourhood. In the spinal roots the organisms were observed passing inwards along the septa. There were many organisms within the adventitial lymph-spaces of both cord and roots, but none within the lumen of the vessels. The vessels were dilated, congested, and the adventitial space infiltrated with small round cells. The organisms within the cord, therefore, find their way into those areas which are affected in toxic diffusion. This is especially well brought out by reference to the case of brachial neuritis, in which it will be remembered the myelin degeneration was distributed in the posterior root entry zone, the anterior radicular zone, under the pia-arachnoid and along the septa to the central parts of the white matter.

This case of organismal infection is of considerable significance. It shows us that the cerebrospinal lymph flows into the adventitial spaces of the vessels, which may thus be infected secondarily. We know, too, that the products of myelin degeneration in many cases may be swept into these spaces until the vessel stains jet black with osmic acid. It is most probable that the unity of the adventitial lymph system with the general lymph circulation in the cord is the true explanation of the vascular phenomena found in acute myelitic lesions, and that these should not be considered as of hæmatogenous but of lymphogenous origin. Strong support in favour of that view will be found in the next series of experiments.

The Histological Evidence of Experimental Infection of the Central Nervous System by the Lymph System of Peripheral Nerves.

Series 1.—The method of experiment adopted was similar to that previously employed. The capsule containing a broth culture of an organism was placed under the gluteus maximus of a rabbit or dog and in contact with the sciatic nerve. The organisms employed for experiment were the *Staphylococcus pyogenes aureus*, a diphtheroid bacillus from a case of general paralysis of the insane, and the *Bacillus botulinus;* the animals were allowed to live for varying periods up to one month. At first we found that movements on the part of the animal caused the capsules to burst; this was reduced to a minimum by using small capsules and thus we obtained tissue free from suppuration.

After the tissue had been placed in formalin 10 per cent. for at least fourteen days, longitudinal sections were made of the trunk of the sciatic nerve in its whole length, and of the lumbo-sacral ganglia with the anterior and posterior roots attached. A portion of the celloidin capsule with the nerve adherent to it was embedded in paraffin, cut transversely, and the sections fixed on albuminized slides. We propose to begin our description with the morbid phenomena at this point and will then pass on to the changes in the epi- and perineurium, to the signs of irritation in the nerve, and finally, to those in the spinal roots and ganglia. The sections were stained either with toluidin blue alone, or counterstained with erythrosin.

A.—Where no Suppuration occurred.

In an experiment of ten days' duration, the inflammatory exudate binds the nerve fairly firmly to the capsule, and is composed of definite layers (fig. 1). In that lying nearest to the capsule there are a large number of polymorphonuclear leucocytes mixed with many cells whose protoplasm is scanty in quantity and whose faintly stained oval nucleus of medium size contains very little chromatin (fig. 2). Many of these clear nuclei are considerably distorted, others are placed excentrically in a cell body of fair dimensions. Excentricity of the nucleus is frequently associated with diminution in size. The second layer is composed almost exclusively of typical fibroblasts (fig. 2). Where it joins the first layer there are small round basophilic bodies suggestive of degenerated polymorphonuclear leucocytes; at its opposite margin are a few lymphocyte-like cells, some clear oval nuclei with little chromatin, and some young fibroblasts whose nuclei though elongated are still oval in contour. This fibroblast layer is intimately connected with the epineurium, which is intensely inflamed.

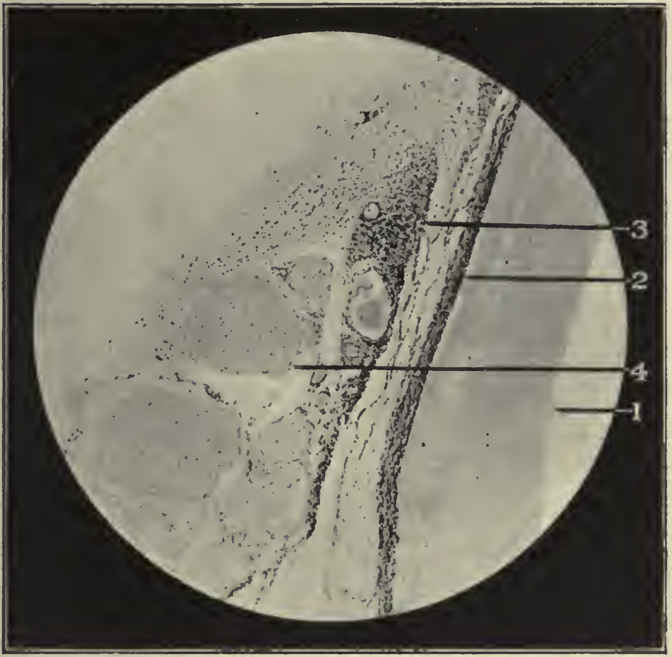

FIG. 1.—1, celloidin capsule; 2, layers of exudate; 3, granulation tissue in epineurium; 4, fasciculi of sciatic nerve.

There is a change in the character of the cellular reaction immediately the line is crossed between the fibroblast layer and the highly vascular epineurium. In this there are a large number of cells around the capillaries and veins; there are also groups of new vessels. With high magnification the adventitial sheath of the veins is seen to be infiltrated with small round cells whose nucleus stains deeply (fig. 3). Many of these surround the smallest vessels and lie free in the intervening tissue. In some, the protoplasmic body is indistinguishable; in many, however, there is a faintly stained narrow ring of cytoplasm; in others, again, the cell body is quite distinct, stains a violet colour, and the nucleus is excentric. Around some capillaries and veins there are typical young plasma-cells with a round, excentric nucleus, a violet vaguely granular protoplasmic body, and a distinct crescentic halo at the central side of the nucleus (fig. 4). As we shall note the presence of plasma-cells frequently, it may be advisable to define what we mean by the term. The body, as a rule, is round, but may be fusiform or cubical according to pressure of numbers or the density of the tissue in which the cells are situated; the protoplasm stains of a blue or blue-violet colour, and we agree with Nissl [24] that while not definitely

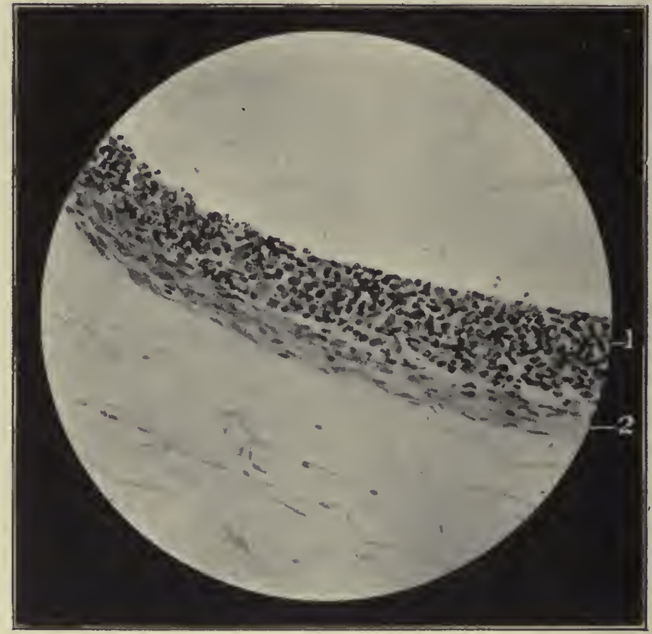

FIG. 2.—1, polymorphonuclear leucocytes mixed with large clear cells; 2, fibroblast layer.

granular, still it is not homogeneous. There is a halo of varying size at the central side of the excentric oval or round nucleus, in which strongly staining chromatin particles may be uniformly distributed, or arranged at intervals round the periphery—the "clock-face" appearance.

In the areas of new vessel formation there are many cells with a large clear oval nucleus scattered amongst the round cells. Sometimes no cytoplasm is visible; the majority, however, possess a small quantity of protoplasm which stains very lightly. In a limited number it is more evident and is drawn out at both ends of the cell as a fine thread, an appearance reminiscent of developing fibroblasts.

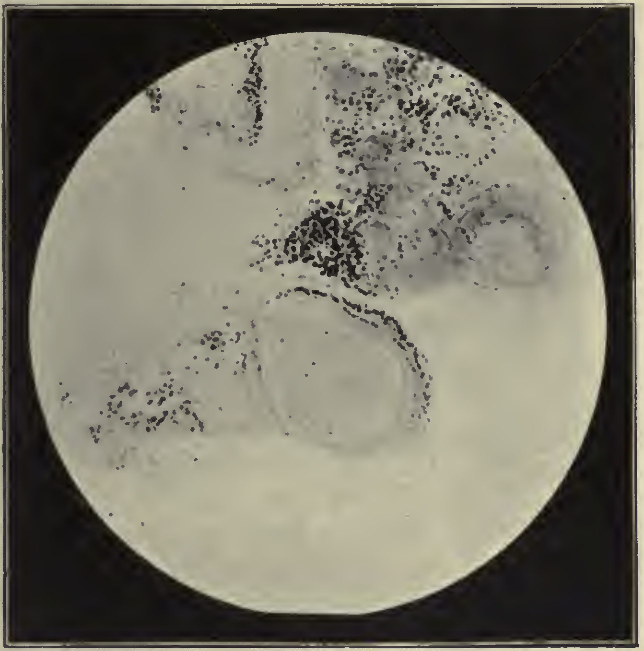

FIG. 3.—Small round-cell infiltration of epineurium and adventitial sheath of a vein.

At the twentieth day much the same phenomena are seen, with, at the same time, some important though slight differences. In the polymorphonuclear layer next to the capsule the cytoplasm of the cells with clear oval nuclei is much more prominent. Some are reticular in appearance with a nucleus of irregular outline. In the second layer the transition from young to adult fibroblasts is very well seen, and is indicated by the progressive flattening and elongation of the nucleus and by the marked increase in length of the protoplasmic body. On the side of this second layer which is nearest the nerve there are groups of reticulate cells, amongst which are a few fibroblasts. These cells possess a large, faintly stained reticular cytoplasm; in some the nucleus is large, pale, and irregular in outline, while in others it is much reduced in size, stains deeply, and is excentric in position.

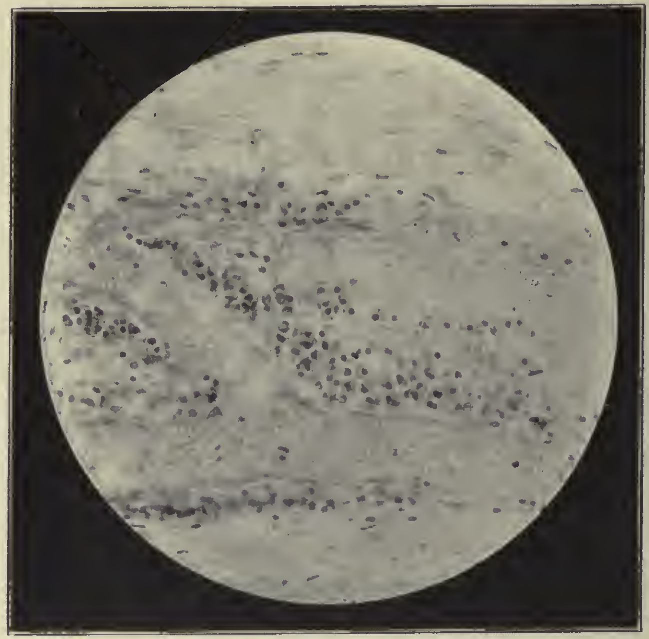

FIG. 4.—Plasma-cells round a vein. Note the absence of proliferation of the intima.

In some experiments the nerve was carefully stripped from the capsule and cut in longitudinal section in order to study specially the reaction phenomena in the epineurium. On the tenth day this highly vascular tissue shows a remarkable degree of inflammation, especially around the veins and capillaries (fig. 5). There are many proliferated nuclei, some of which are small, round, and deeply stained; others, again, are large and pale, with fine granules of chromatin. The majority of the pale nuclei are oval in shape and regular in outline; some, however, are more elongated or pear-shaped, and in others the nuclear membrane may be irregular or indented. The round, darkly stained nuclei occur in large numbers, and there are plasma-cells in all stages of development amongst them. Many of these plasma-cells do not stain quite normally, and occasionally some are seen in a regressive phase in which the body is pale and hyaline, while the nucleus stains deeply and is crenated. The intima of the vessels around which this proliferation is occurring is comparatively free from irritative phenomena; all that is seen is swelling of the endothelial nuclei which may project into the lumen or become detached. Occasionally, there are small collections of polymorphs and lymphocytes to be seen in the vessels and lying at the periphery of the blood-stream; this is the only evidence of participation of the hæmatogenous elements in the inflammatory process. The connective tissue nuclei of the areolar reticulum are pale, swollen and distorted, and there are plasma-cells lying, not only amongst them, but free in the spaces.

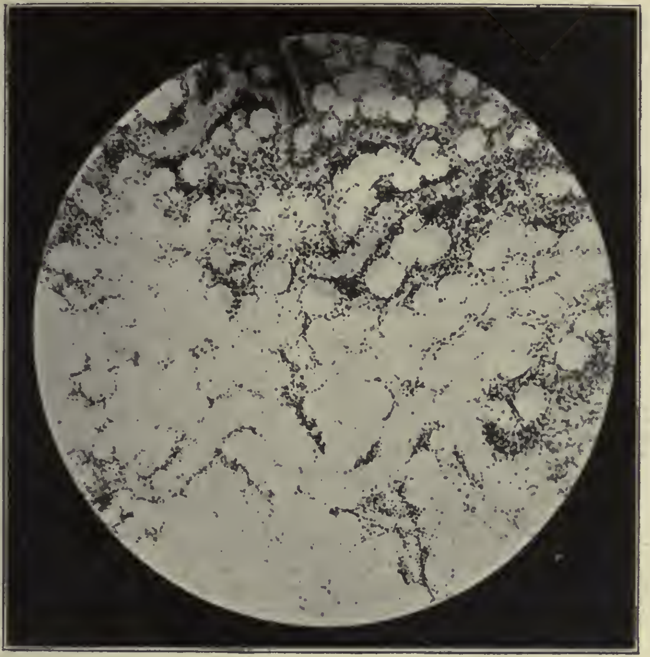

Fig. 5.—Proliferation of adventitia of veins in the epineurium.

If the section happens to pass longitudinally through the adventitial coat alone a clearer estimate of the degree of proliferation in this sheath is obtained than if the lumen is included. The adventitial spaces are filled with a mass of cells possessing large clear nuclei of almost every conceivable shape, and with plasma-cells in all stages of transition. In many of these the protoplasmic body is quite typical, but the nucleus, though excentric, is oval and clear and quite indistinguishable from a reacting adventitial nucleus. There are other plasma-cells of a more elongated type which somewhat resemble fibroblasts.

The degree of proliferative change in the perineurium is considerable. It is filled with clear nuclei of varying shape, round, oval, elongated and narrow, and irregular. The cell reaction is less in the inner layers. Amongst the proliferated nuclei are numerous plasma-cells, whose shape varies considerably, probably on account of the pressure exerted by this dense lamellar tissue. Many are triangular, others markedly elongated. All show the characteristic vaguely granular body with the halo. They are a constant feature in the adventitia of the capillaries and veins, which always show proliferation.

By the twentieth day the inflammatory reaction has changed greatly in character. In the epineurium there are many round or oval medium-sized nuclei of varying staining reaction. There are also numerous plasma-cells of which many are undergoing regressive changes; their nucleus and cell body are often pale, the halo is still perceptible, but the remainder of the cytoplasm is uniformly granular, and at the edge of the cell irregular. Occasionally at this stage the protoplasmic body is vaguely reticular. Side by side with these plasma-cells are numerous clear, hyaline, reticular cells with a small excentric nucleus frequently deeply stained. Young fibrous tissue cells are also present. Plasma-cells are very numerous in the perineurium and also in the adventitia of the veins which surround the nerve and pass into the septa between the bundles; they are typical morphologically, and are arranged in rows along the adventitia, whose nuclei are proliferated and stain rather feebly.

One inch above the upper end of the capsule there is in the sheath of the sciatic nerve a considerable diminution in the degree of inflammatory reaction. There are many proliferated nuclei in the epineurium, which are almost all oval in shape, and form small groups. Plasma-cells are rarely found lying free in the areolar spaces. The adventitial cells of the veins are enlarged, proliferated, usually oval in outline, and amongst them are many plasma-cells in all stages of development. These are not quite so large here as in the portion of nerve which lies on the capsule. Often their protoplasm is scanty, or irregular in outline, the halo narrow and more like a perinuclear ring; where several are in apposition they may be cubical, but in all the cytoplasm is vaguely granular and the chromatin particles in the nucleus, which may or may not be central, are arranged in "clock-face" fashion. Associated with them are round nuclei rich in chromatin without a visible cell body, or with the merest trace. The endothelial cells of the veins are frequently swollen.

The veins and capillaries within the nerve are much less affected than in the perineurium, and the inflammatory reaction is of a more sub-acute nature. The reaction in the capillaries is very variable, but always very definite (fig. 6). The adventitial nuclei are swollen, and in the spaces are many small, round, dark nuclei, around some of which is a moderate quantity of vaguely granular protoplasm; there is also a narrow perinuclear space. Quite frequently, and in connexion with the finest vessels, plasma-cell formation is the predominant feature. These are, as a rule, arranged in a row along the vessel wall, and exhibit all phases of transition from the youngest to the mature forms. The endothelial nuclei frequently show a considerable degree of swelling.

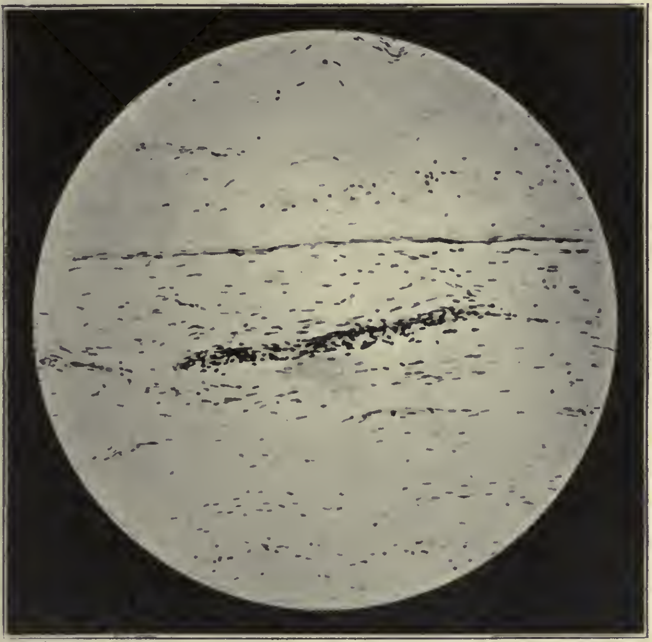

FIG. 6. Capillary within the nerve. Proliferation of adventitial cells.

There is abundant evidence of irritation just distal to the sensory ganglia, in the ganglia themselves, and in the spinal roots of the lumbosacral enlargement. The nuclei of the cells of the ganglion capsule are swollen and in places proliferated. Round the veins there are groups of plasma-cells. These are also present in the adventitial sheath, whose nuclei are increased in number. A group of fully developed plasma-cells is often seen at the proximal pole of the ganglion just where the anterior and posterior roots diverge. Their relation to a vein is sometimes obvious, and hæmorrhage may be present with them. The capillaries of both roots and the ganglion show the same changes as described in the fasciculi of the sciatic nerve. The adventitial nuclei are proliferated, are round or oval, and in some the chromatin is arranged similarly to that in the nuclei of the plasma-cells of which there are many examples in all phases of development.

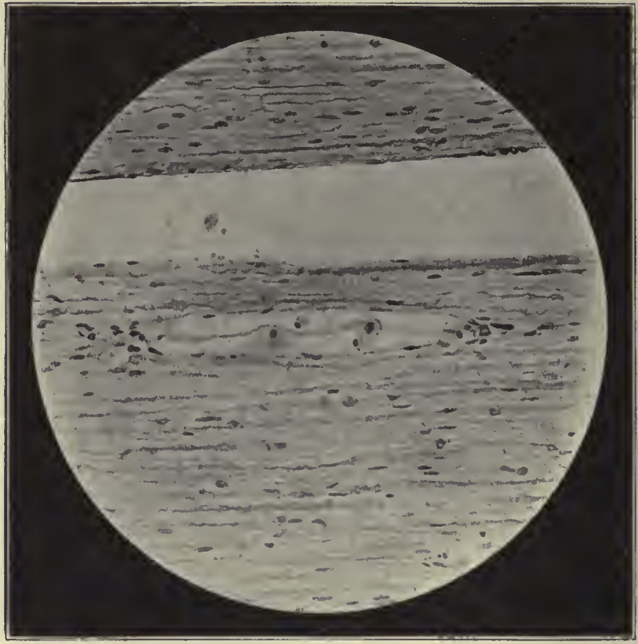

Fig. 7.—Posterior spinal root. Note the area of degenerate dmyelin. The axis cylinder is surrounded by compound granular corpuscles.

Chromatolysis of the ganglion cells is rare and when present is of the peripheral type. The nuclei of the nerve-cell capsule are proliferated, and at times invade the outer zone of the nerve-cell.

If we *summarize* the above phenomena we see an inflammatory reaction in the sciatic nerve which is continued through the sensory ganglia and along both spinal roots (fig. 7). The toxins induce inflammation of the fixed tissues, such as the epineurium, the perineurium, and in the veins and capillaries outside and inside the nerve; no reaction has been observed in connexion with the arterioles. There is a marked diminution in the severity of the inflammation as soon as the immediate neighbourhood of the toxic focus is left. The hæmatogenous elements do not participate in the process, and the very slight involvement of the intimal cells is noteworthy.

To put the cellular reaction briefly, we have, proceeding from the capsule:—

(1) A layer of polymorphonuclear leucocytes mixed with large clear nuclei.

(2) Developing and adult fibroblasts amongst which are clear nuclei similar to those in layer (1).

(3) In the epineurium, new vessel formation, clear nuclei of proliferating adventitia, round dark nuclei, and plasma-cells in all phases of development.

(4) In the inner layers of the perineurium a marked diminution in the degree of inflammation. The cells of the lamellæ are proliferated; there are many plasma-cells.

(5) One inch above the capsule there is much less reaction in both the epi- and perineurium.

(6) Within the nerve the inflammatory phenomena are very slight as compared with those in the nerve-sheath. Plasma-cell formation, especially in connection with the capillaries, is the most prominent feature. Similar vascular changes are seen in the posterior root ganglia and spinal roots.

In the polymorphonuclear layer and in the epineurium there are many reticulate cells. Many of the plasma-cells show regressive phases; their cell body becomes pale and hyaline, while the nucleus undergoes shrinkage.

B.—Where Suppuration occurred.

When through rupture of the capsule the organisms escaped there was most intense inflammation of the nerve. The layer next the capsule is composed of groups of organisms, polymorphonuclear leucocytes, many of which are degenerate, and numerous cells with a large clear nucleus surrounded by a varying quantity of protoplasm. Outside this layer there is a broad band of fibroblasts arranged in parallel rows, and in the epi- and perineurium a high degree of proliferation in the fibrous structures and vessel-sheath.

The proliferative reaction in the nerve-sheath decreases from without inwards. In the inner layers the laminar arrangement of the fibrous tissue is maintained, though the cells are elongated and swollen. In the outer layers the cells assume a variety of shapes. Some are elongated, in others the protoplasm shows no definite edge and lies to one side of the nucleus. Sometimes the protoplasm is collected in a mass round a central nucleus, or the nucleus may be excentric and the protoplasmic body possess several processes streaming away from it. There are many new formed vessels, some of which can be traced from the epineurium almost to the capsule. Their walls consist of one or more layers of elongated cells, with a pale fusiform nucleus and some protoplasm streaming from either side of it. Some of these cells are actively proliferating and wander into the surrounding tissue. Plasma-cells are few, and are seen only in the neighbourhood of the vessels of the epineurium.

In sections of the nerve just above the site of the capsule there is still proliferation of the epi- and perineural sheaths, but it is less active. Cell proliferation in the walls of the vessels is a striking feature, but it is limited to the veins and capillaries. The adventitial sheath shows the most pronounced change. The intimal cells are swollen, and in the majority the nucleus is pale and fusiform. At times, however, they are rounded and project into the lumen. With this the whole cell stains more deeply than normal. Multiplication by direct division may be observed frequently. As mentioned above there is marked proliferation of the adventitial elements. The nucleus is usually pale and oval, and the protoplasm may be concentrated around it or extend outwards on each side. Some assume the characters of fibroblasts and pass from the vessel wall into the fibroblast layer. Amongst the proliferating adventitial cells another type is evident. It possesses a rounded and deeply stained nucleus whose chromatin is uniformly distributed or arranged around the nuclear membrane. The protoplasm may be scanty, lie to one side of the nucleus or surround it, and be separated from it by a clear zone. Other cells show all the morphological characters of the adult plasma-cell, and these with their intermediate forms occur in large numbers in the adventitia of all the veins and capillaries, and also amongst the fixed connective tissue cells of the areolar tissue in the epineurium (fig. 8).

Two inches above the seat of maximum intensity there is a decided change in the character of the reaction. The adventitial sheath of the veins is filled with plasma-cells at different stages of development, and the intimal cells may be normal or show a slight degree of swelling. In the capillaries the intimal reaction is often more prominent than in the veins. Many of the plasma-cells show retrograde change in which the nucleus is small and darkly stained, while the protoplasm is hyaline, vacuolated, or reticulate.

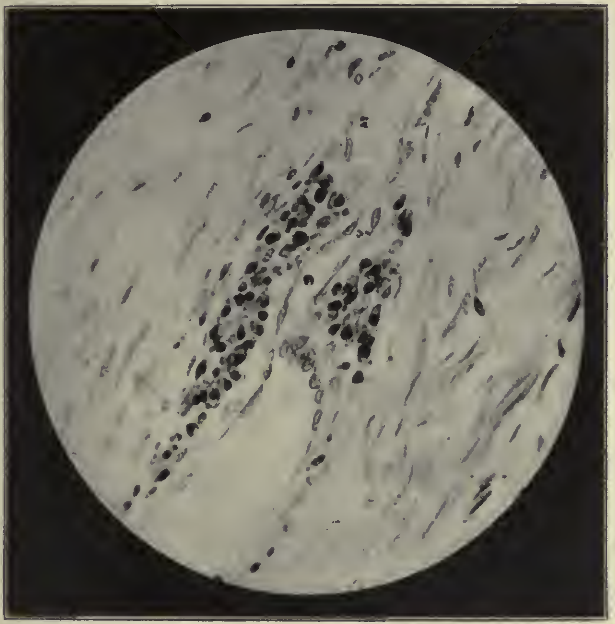

FIG. 8.—In the centre, plasma-cells round a venule of the perineurium; at the edge, young fibroblasts.

In the posterior root ganglia the capsular cells round the nerve-cells are increased in number, and the nerve-cells exhibit various stages of chromatolysis, or coagulation necrosis with homogeneous atrophy of the nucleus.

The appearances in B differ broadly from A in the much greater formation of fibroblasts, the larger number of new formed vessels, and the greater degree of reaction in both adventitia and intima.

Series 2.—In this series of experiments the capsule containing organisms was placed in a position much nearer the cord in order to diminish the distance along which infection had to travel to it. The *Staphylococcus pyogenes aureus* was employed and two situations were selected for operation. In one the spinal cord was laid bare at the level of the lumbo-sacral enlargement and a capsule was fixed against the dura mater; in another the muscles were separated from the vertebræ in the dorsal region and a capsule placed against an intervertebral foramen. All the experiments gave positive results, which varied, however, in degree, as in some the capsule ruptured and the organisms spread to the dura mater.

The rabbits operated on lived for a period varying from three days to three weeks. The spinal cords were fixed in absolute alcohol for the toluidin blue and pyronin-methyl-green stains, and in Weigert's chrome-alum-copper solution for the Alzheimer and Mallory stains. The tissues were examined in transverse and longitudinal section.

In our description we begin with the reaction in the capsule of the posterior root ganglia and the dura mater, with which it is continuous; then, passing inwards, take up the inflammation in the spinal roots, the pia-arachnoid, the white and grey matter of the spinal cord. Longitudinal sections are especially useful in tracing the reaction from without inwards, because it is possible in the same section to compare the degree of intensity of the inflammatory process between one part and another in unbroken continuity from the sensory ganglion to the centre of the spinal cord. It will be seen that the reaction diminishes from without inwards, and that the dura mater and perineurium with their covering of highly vascular areolar tissue form a most efficient protection to the spinal cord and neutralize the effects of infection to a considerable extent.

A.—Where no Suppuration occurred.

It is not necessary to describe the reaction in the ganglion capsule and the dura mater separately, as they are continuous. The inflammatory changes could be followed along the areolar tissue lying on the ganglion surface, and thence on to the outer surface of the dura. The spaces of the epidural tissue are filled with inflammatory products, the vessels are widely dilated, and there are hæmorrhages. The greater proportion of the exudation is composed of round mononucleated cells, amongst which are scattered the residue of degenerated polymorphonuclear leucocytes. The cell body of the mononuclears stains deeply with toluidin blue and intensely red with pyronin-methyl-green; it is round in the majority, oval in others, and the contour is irregular in practically all. Its peripheral portion stains more deeply than the centre, and vacuolation is a constant feature. Many of these cells show advanced phases of degeneration in which the cytoplasm is reduced to shreds and the nucleus is pale and distorted.

The appearance of the nucleus varies very considerably. Sometimes it is small and deeply stained, at others it is larger and clearer. It may be central or excentric. The arrangement of the chromatin is not constant; in some nuclei it is situated round the membrane, in others it is scattered throughout. Degeneration of these nuclei is common, when they stain diffusely and are irregular in outline. There are a large number of cells resembling small lymphocytes present, and compound granular corpuscles, with the typical fenestrated cytoplasm and the small dark excentric nucleus. Between the latter and the mononuclear cells there are many transitional forms. Mitotic figures occur in some of the cells, and giant cells are found in considerable numbers (fig. 9).

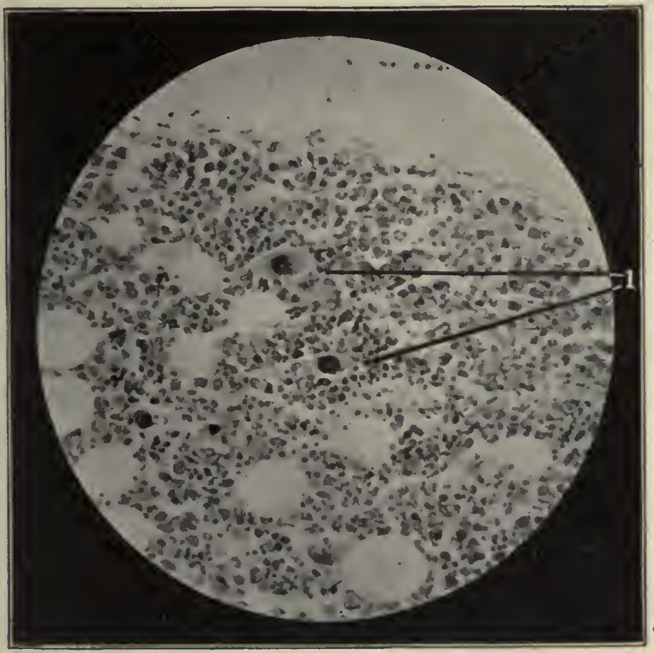

FIG. 9.—Inflammatory reaction in the epidural tissue: polyblasts, lymphocytes, reticulate cells, &c.; 1, giant cells.

The adventitia of the veins of the epidural tissue is infiltrated with plasma-cells, all of which, however, are not fully developed. Here and there around the veins are small collections of cells resembling lymphocytes. The nuclei of the areolar tissue cells are pale and swollen, and where the fibrous strands meet one often sees cells whose body is rounded and shows a small halo on one side of the nucleus.

Very distinct evidence of toxic invasion of the dura mater and ganglion capsule is seen from the presence of numerous plasma-cells between the fibrous tissue layers, and in the adventitial lymph spaces of the veins (fig. 10). There are no polymorphonuclear leucocytes or mononuclear cells present. Many of the nuclei of the dural cells are swollen and oval in shape, and, from these, plasma-cell formation can be traced through transitional forms. Within the root ganglia there are many plasma-cells lying free, collected into small groups, or in the adventitia of the veins and capillaries. The reaction phenomena are greater in degree at the proximal pole of the ganglion where there is a large group of plasma-cells at the point where the spinal roots diverge (fig. 11). Their relation to a vein and to hæmorrhage in this situation is noteworthy. At this point and along the anterior and posterior spinal roots

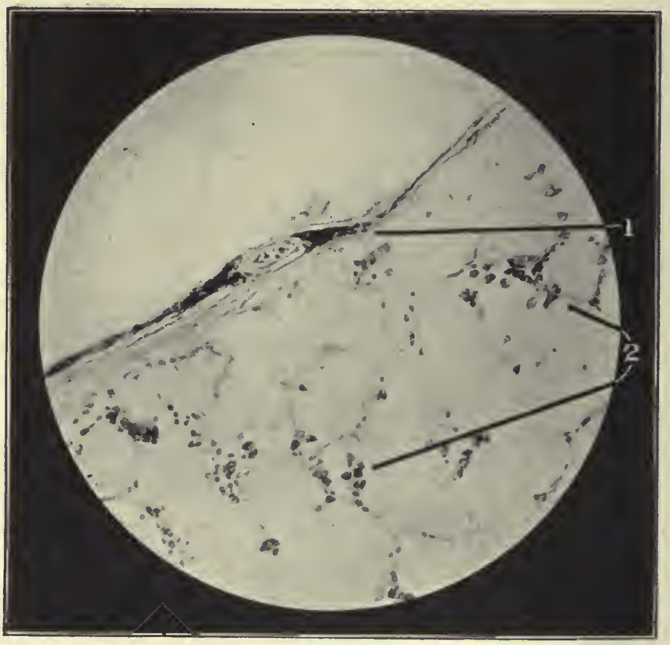

FIG. 10.—1, collection of plasma-cells round a vein in the dura mater; 2, proliferation of trabecular cells of epidural tissue.

inflammatory changes of varying degree are present in the adventitial sheath of the small veins and capillaries, and in the perineurium there are chains of plasma-cells extending from the ganglion to the spinal cord (fig. 12). The adventitial nuclei show signs of reaction. They diminish in size and become rounder and darker. As the cytoplasm increases in quantity the nucleus stains less deeply. Scattered amongst the adventitial nuclei are adult plasma-cells.

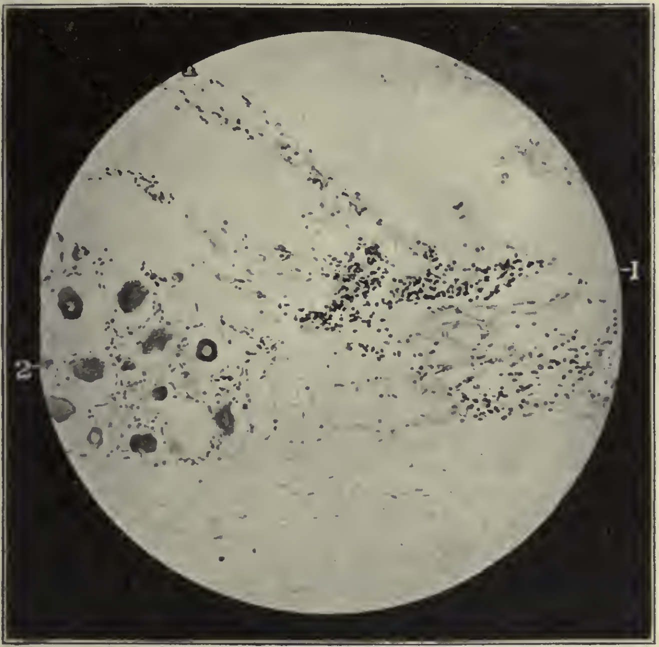

FIG. 11.—1, collection of polyblasts and plasma-cells at the proximal pole of the root ganglion ; 2, root ganglion nerve-cells.

The degree of reaction in the pia-arachnoid and cord is much less than in the ganglia and spinal roots, and from the pia inwards there is a progressive diminution in the intensity of the inflammatory phenomena. The nuclei of the cells lining the trabeculæ of the pia mater are in many instances swollen and stain more deeply than normal. The adventitial cells of the veins and capillaries are greatly increased in number, are small, round and deeply stained, while plasma-cells in all stages of development are evident. This reaction is especially well seen in the small vessels passing from the inner layer of the pia into the white matter. In transverse sections vessels showing these

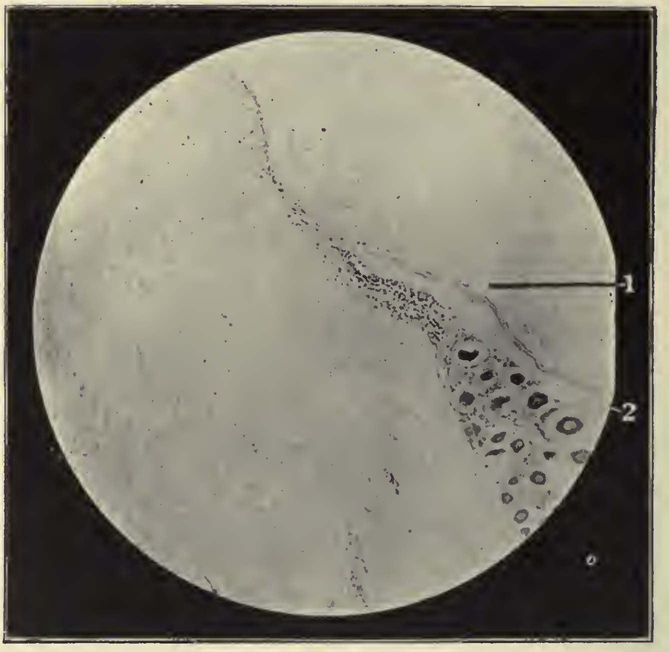

FIG. 12.—1, inflammatory reaction in the perineurium between the root ganglion and the cord; 2, root ganglion nerve-cells.

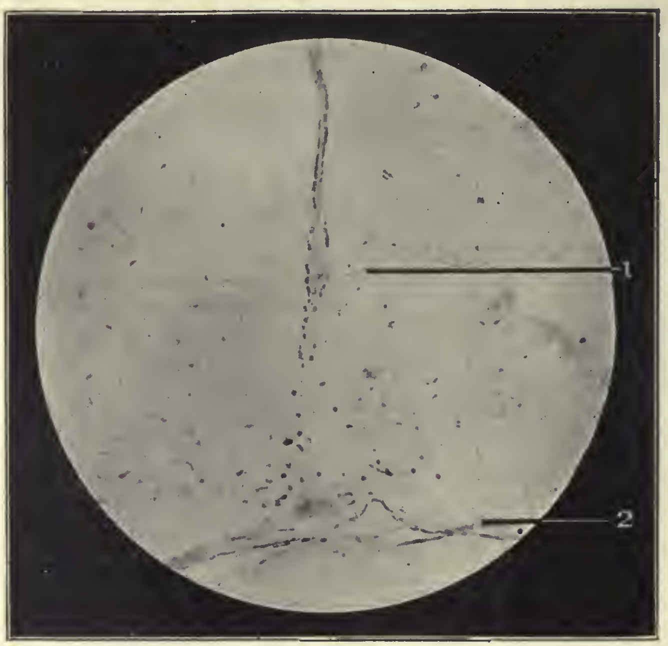

FIG. 13.—1, plasma-cells in the adventitial sheath of the vein in the postero-median septum of the cord; 2, pia-arachnoid.

changes are observed dipping into Lissauer's tract, the substantia gelatinosa Rolandi, the root entry zone, along the postero-median fissure, down the septa into the lateral region as far as the basis bundles, and through the area of the emerging anterior roots (fig. 13). Reaction changes are found in connexion with the vessels of the grey matter also, but trifling as compared with those of the peripheral portions of the spinal cord. The adventitial sheath of the veins and capillaries in the outer portion of the grey matter exhibits proliferative changes and is infiltrated with young plasma-cells, but near the central canal the reaction is minimal. Here the adventitial nuclei are merely rounder and more deeply stained than normal, while at times the endothelium projects into the lumen.

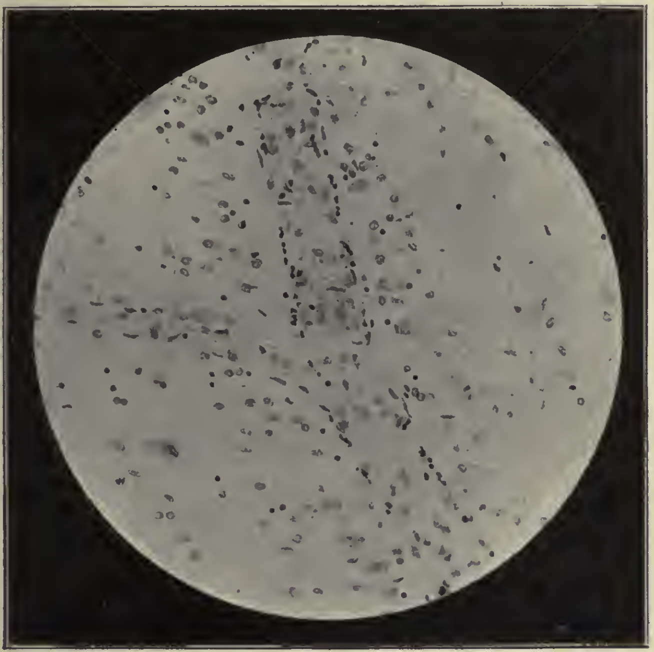

FIG. 14.—Note the proliferation of neuroglia round the venule.

The neuroglia elements throughout the cord are proliferated, especially in the neighbourhood of the venules and capillaries in the white matter. By Alzheimer's method the nucleus is clear, round or oval; the cytoplasm stains light blue, is increased in quantity, and often extended into short stumpy processes. These are the "amœboid" glia-cells which are characteristic of acute morbid processes. In toluidin blue sections the proliferation of glia around the vessels is seen to be going on actively. A longitudinal section of a vessel shows a healthy endothelium, or nearly so, an adventitial sheath filled with darkly stained nuclei and young plasma-cells, and, separated by a clear space, a row of proliferated "amœboid" cells (fig. 14). In the grey matter the glia shows much the same change as in the white. The cells sometimes form small collections of four, five or even ten elements in the vicinity of the nerve-cells.

The large majority of nerve-cells are normal. No change is to be observed in the large cornual cells, but some of the smaller are pale and exhibit chromatolytic change. There is little change in the nerve-cells of the posterior root ganglia. In some there are regressive alterations of a mild nature and a few are invaded by round or oval clear nuclei. The cells lining the central canal are not affected.

The reactive changes induced by this series of experiments may be summarized briefly as follows:—

(1) In the epidural tissue; polymorphonuclear leucocytes, plasma-cells, and mononuclear elements similar to those termed polyblasts.

(2) Plasma-cells in the dura mater; in the capsule of the posterior root ganglion and within it where they form a prominent group at the proximal pole; in the perineurium of the spinal roots and in the adventitial sheath of their vessels; in the pia mater, and in the adventitial sheath of the vessels passing into the spinal cord.

(3) Proliferation of the neuroglia-cells.

B.—Where Suppuration occurred.

In the experiments in which a capsule was placed against an intervertebral foramen the organisms escaped and an abundant growth occurred in the surrounding tissues. From the site of the capsule the organisms could be followed along the nerves to the posterior root ganglia and onwards to the dura mater. The spread of the organisms was accompanied by active proliferation of the cells of the perineurium and a leucocytic exudation. The majority of the cells were degenerated.

There are many organisms in the areolar tissue covering the ganglion capsule and the dura mater. Here the inflammation is intense. The cells of the ganglion sheath, of the dura mater, and of the adventitia of the veins in those tissues are proliferating actively (fig. 15). Some of the proliferated cells have all the characters of fibroblasts, in others the nucleus is more rounded and the cell body larger. Others again, with a paler nucleus, resemble large lymphocytes. Many degenerate forms are present. There is a high degree of proliferation of the capsular cells round the nerve-cells of the spinal ganglia, which exhibit acute chromatolytic changes.

The pia-arachnoid is acutely inflamed, and the cells of the exudate have an elongated oval shape and a nucleus moderately rich in chromatin. In the adventitia of the veins at the margin of the cord the reaction cells are rounder and their nuclei show variations in shape and staining quality. The majority of the nuclei are pale; a few are deeply stained. At times they are round, but generally oval, with an indentation on one side. Most of the cells possess a considerable quantity of protoplasm, but those with a round dark nucleus have little, and resemble small lymphocytes (fig. 16).

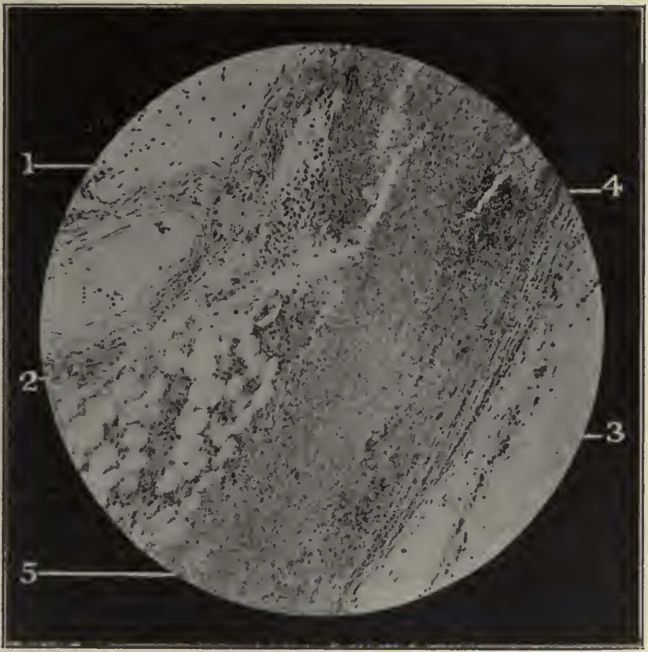

Fig. 15.—Inflammatory reaction outside dura. 1, posterior spinal root; 2, proliferation of cells of adventitia of a perineural vein; 3, lateral column of spinal cord; 4, proliferated cells of dura mater; 5, inflammatory reaction and organisms in epidural tissue.

The efficiency of the dural barrier to the inward spread of organisms is well illustrated in these experiments. Only rarely did they reach the pia-arachnoid. When this did occur the organisms could be traced into the adventitia of the veins of the lateral columns of the cord. A vein thus infected shows many degenerated cells in its adventitia close to the pia-arachnoid. Further inwards the reaction cells are better preserved and both adventitial and intimal cells are in a state of active proliferation (fig. 17). Their nuclei are round or oval, and in many cases show an indentation on one side; the cell sometimes contains a few irregularly distributed, deeply stained masses. Frequently the nucleus is so much indented and irregular in form as to resemble that of a polymorphonuclear leucocyte. Cells of this type have been described by Wickmann [43] in his work on acute poliomyelitis as "polyblasts."

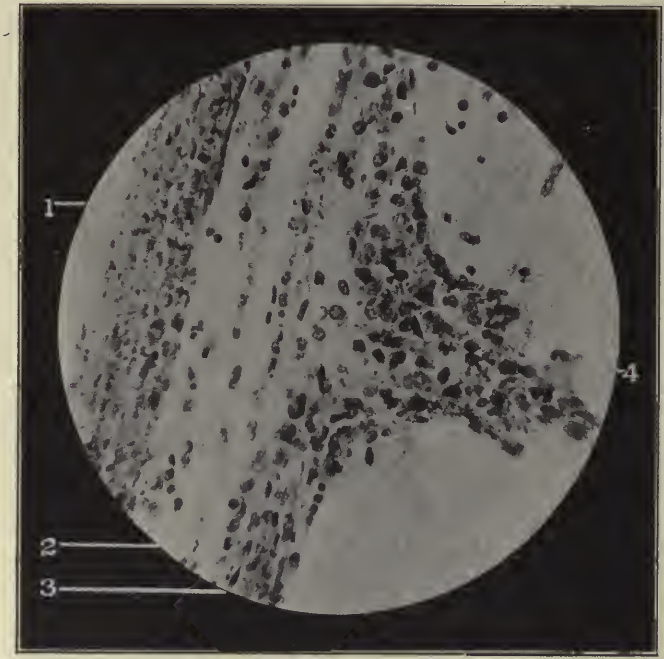

Fig. 16.—1, Organisms in epidural tissue; 2, proliferation of cells of dura mater; 3, proliferation of cells of pia-arachnoid; 4, proliferation of adventitial cells of a vessel passing into the lateral columns, with formation of polyblasts.

In connexion with some of the vessels there are collections of cells which present quite a different appearance. Their nucleus varies in size and staining reaction. Most are round, deeply stained, and situated at one edge of the cytoplasm, which also shows variations. Frequently it is obviously reticulate, and the spaces in the meshwork may be clear, or occupied by a material which stains somewhat less deeply than the

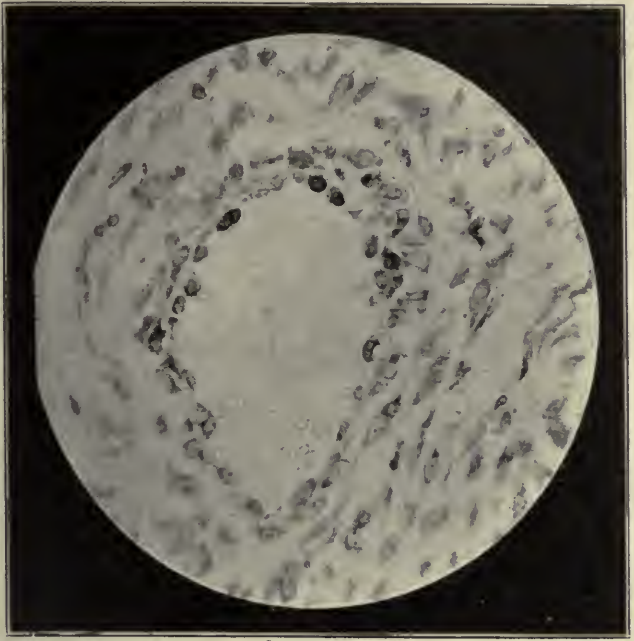

FIG. 17.—Proliferation of intimal cells, showing their projection into the lumen of the vessel.

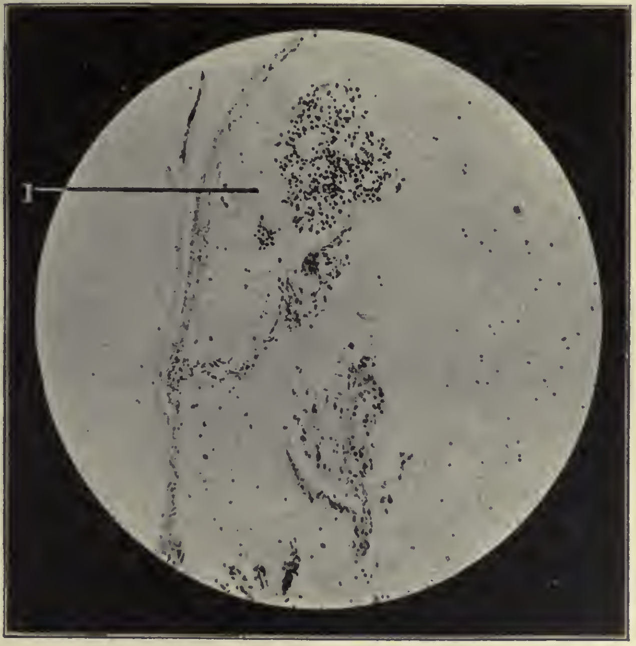

FIG. 18.—(1) Collection of compound granular corpuscles.

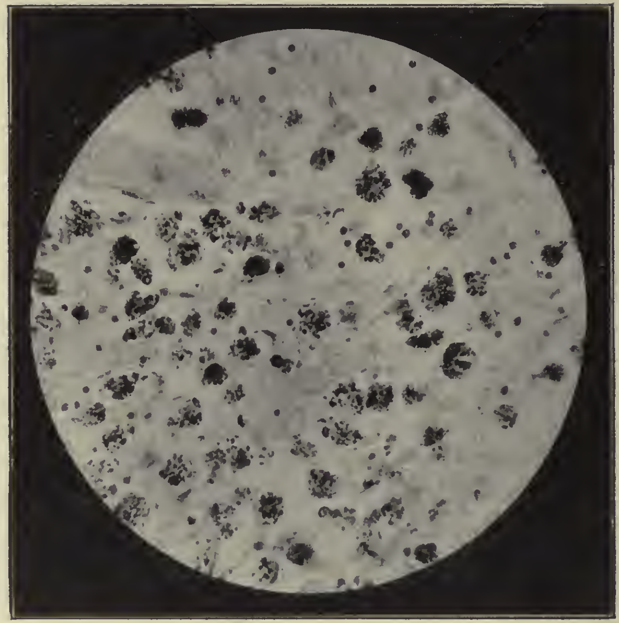

Fig. 19.—Compound granular corpuscles. (Körnchenzellen.)

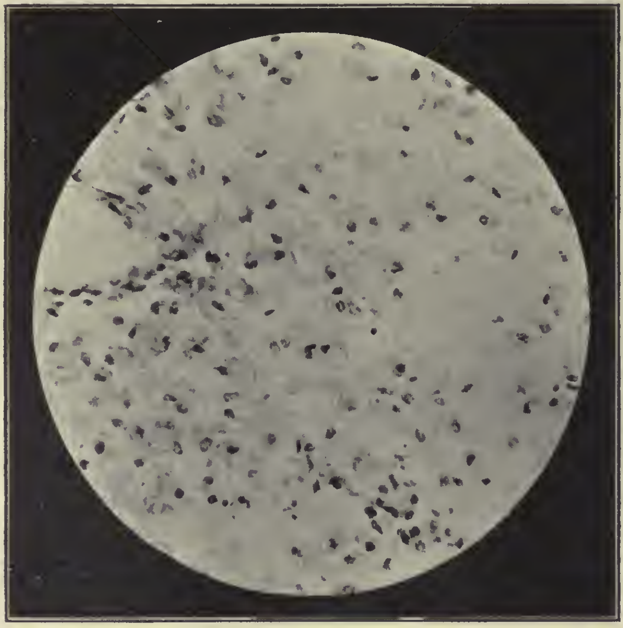

Fig. 20.—Reticulate cells.

nucleus. These cells correspond morphologically with the epithelioid cells and "Körnchenzellen" of Friedmann [11] and their function is that of removing the products of degeneration. Their significance will be discussed later (figs. 18, 19, 20).

Although it is rare to meet with organisms within the spinal cord, it is important to note that the vessels in both grey and white matter are the seat of marked pathological changes. They are dilated, and their walls are infiltrated with round cells (fig. 21). In some there are fibrin filaments. Hæmorrhages are seen occasionally. The infiltration of the vessel walls is more pronounced in the white matter; many of the small vessels in the grey horns show only a degree of dilatation and swelling of their endothelial nuclei.

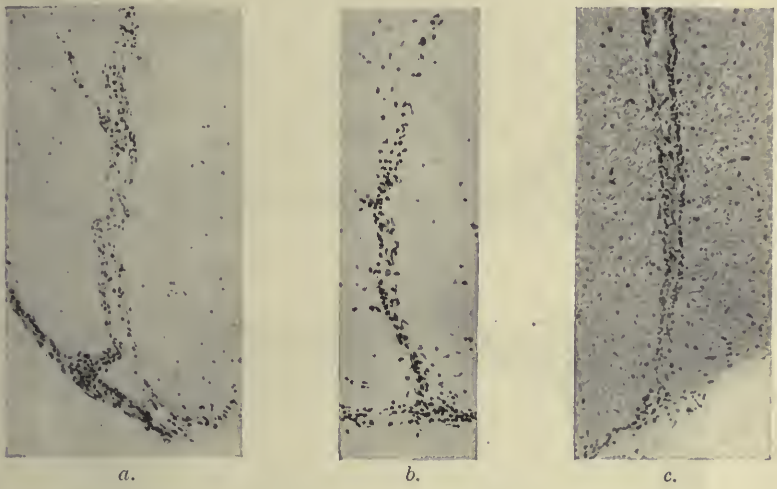

FIG. 21.—Three vessels showing adventitial proliferation: *a*, from experimental lymphogenous infection (cord); *b*, from a case of erysipelas of the face with ascending perineuritis of the fifth nerve (pons); *c*, from experimental acute poliomyelitis in the monkey (cord).

There is a general neuroglia reaction particularly marked around the vessels, and the cells show transitional forms between the normal cell and the "amœboid" type of Alzheimer [3] (fig. 22). The nerve-cells are acutely degenerated. The majority stain very faintly and diffusely; in some the cytoplasm is in a condition of coagulation necrosis with homogeneous atrophy of the nucleus (fig. 23). Many of the nerve-cells are greatly disintegrated and neuronophagy is common. By Marchi's method there is evidence of much fibre destruction in the lateral columns of the cord.

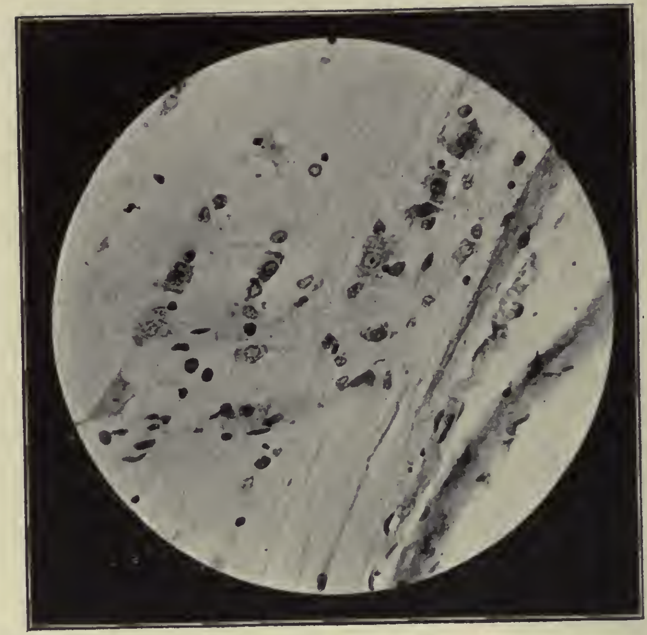

FIG. 22.—Reaction of neuroglia cells: amœboid type of Alzheimer.

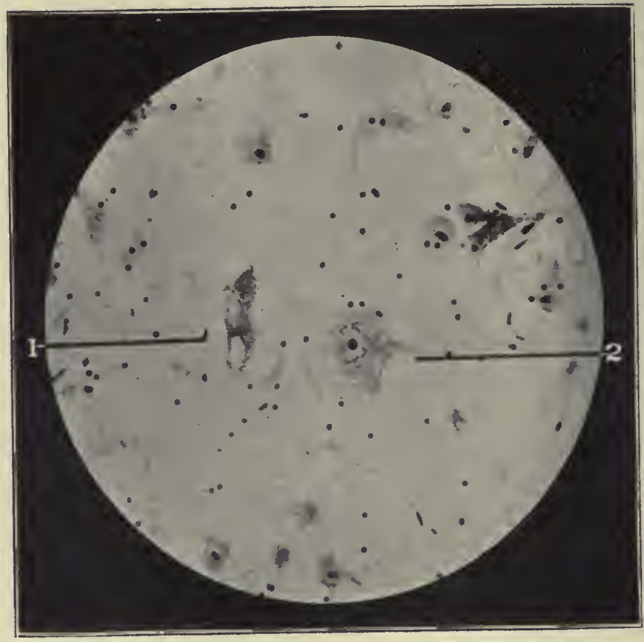

FIG. 23.—(1) Vacuolation of nerve-cell; (2) homogeneous atrophy of the nucleus.

On comparing the phenomena in B with those in A, we find that although they differ very considerably in degree, they have one feature in common, viz., the anatomical distribution of the inflammation.

The evidence given in Series I and Series II leaves no room for doubt that the lymph-stream in nerves is an ascending one, and that toxins and organisms can be carried to the cord by that path. The reaction of the tissues to the toxin also shows that the lymph not only ascends in the spaces of the nerve-sheaths, but diffuses in the fibrous septa between the nerve fasciculi and into the adventitia of the vessels. From the experiments, too, it is clear that when the toxin gains the spinal cord it is carried round the periphery in the meshes of the pia-arachnoid and along its prolongations into more central parts. It is exceedingly interesting to observe how the character of the inflammation undergoes progressive changes from the focus of greatest intensity onwards; and there is one important fact to which we would draw attention and that is how plasma-cell formation becomes the most prominent indication of irritation when the irritant has been to a great extent neutralized by the reaction of the tissues close to the capsule.

The proliferation of the adventitial sheath of the veins and capillaries with plasma-cell formation shows that its lymph spaces communicate directly with the lymphatic system of the nerves and cord; and though, doubtless, the adventitial lymph system of the arterioles has a similar connection, yet the intense reaction around the veins and capillaries points to these as being the principal channel by which the lymph regains the general circulation. This opinion receives support from researches carried out by other methods, such as the injection of coloured fluids into the sub-arachnoid space; these find their way rapidly into the adventitia and thence into the blood-stream. According to Lewandowsky [17], the veins, capillaries, and Pacchionian bodies are the channels by which the cerebrospinal lymph is returned to the general circulation. The reason why the adventitia of the veins and capillaries of the nervous system in lymphogenous infection should show so much inflammatory change is therefore obvious.

The results of the above experiments show that infection of the lymph system of peripheral nerves is followed by an ascending perineuritis which spreads to the posterior root ganglia and along the spinal roots to the cord. The loose areolar tissue covering the perineurium, the ganglion capsule, and the dura mater shows the greatest degree of inflammation. The *clinical cases* which we are now about to bring forward have confirmed the results of our experiments, and it will be observed that not only is the same path of infection clearly demonstrated, but also a perfect similarity in the type of reaction. This reaction varies with the degree of intensity of the irritant.

We propose to give here a digest of these clinical cases: a fuller account has appeared in a previous publication—written in collaboration with Dr. Stephenson [32].

(1) *Carcinoma of the tongue with suppuration in the floor of the mouth.*—The tissues examined microscopically were the twelfth, seventh and fifth cranial nerves; the pons and medulla; the spinal cord; the nerves and posterior root ganglia connected with its cervical portion. In the twelfth and seventh nerves there is a well marked perineuritis. The cells of the exudate possess a round or indented nucleus containing little chromatin, and a faintly stained cell body. Other cells are present with a deeply stained nucleus and a small quantity of well stained protoplasm. The cells of the adventitial sheath of the veins and capillaries in the epi- and perineurium are proliferated. In some of the capillaries the endothelial cells are swollen, round, and project into the lumen. Within the nerve the reaction is much less intense. The neurilemma cells are swollen, and plasma-cells are present in the adventitial spaces. Around the nerve-cells in the geniculate ganglion of the seventh nerve there is proliferation going on amongst the capsular cells. A perineuritis is still present at this level, though it is not so acute as in the more peripheral portion.

The highest degree of inflammatory reaction is round the fifth nerves outside the dura mater, and in the Gasserian ganglia. The peri- and epineurium are infiltrated with polyblasts and cells of the small round lymphocyte type. Between these two are transitional forms. There are also reticulate cells containing refractile granules which stain purple with toluidin blue. They are numerous where hæmorrhage and blood pigment are present, and are probably scavenger cells. Possibly these granules, which at times escape from the cell through the bursting of the cell membrane, correspond to the hæmosiderin observed by Bonfiglio [6] in plasmatocytes of the central nervous system.

Within the Gasserian ganglion there is less reaction than around the nerves. The polyblasts are fewer in number, and larger, rounded, well stained cells with a darkly stained nucleus are present. These resemble the pseudoplasma-cells of Pappadia [33]. Plasma-cells are present; the capsular cells round the nerve-cells are proliferated and while some of the latter show coagulation necrosis with homogeneous atrophy of the nucleus, in others there is advanced chromatolysis and neuronophagy.

The degree of irritation in the pia mater covering the pons is much less than in the structures already described. There is infiltration with small round cells, some of which exhibit the characters of plasma-cells. The same appearance is seen in the adventitial sheath of vessels passing into the pons. The pontine vessels are markedly dilated: the nerve-cells show chromatolysis; and the neuroglia-cells are proliferated.

There is an intense perineuritis of the ganglia and spinal roots of the cervical region. The inflammatory phenomena are most evident in the epidural tissue and at the proximal pole of the ganglion. Within the dura mater the reaction is of less degree. The pia-arachnoid is infiltrated by lymphocyte-like cells, but some plasma-cells are present; the infiltration reaches its maximum in the cervical and upper dorsal regions. The vessels within the cord are dilated and their adventitial cells proliferated.

(2) *Erysipelas of the face.*—The disease ran a course of five days' duration. The fifth cranial nerve, the Gasserian ganglia, and the pons were examined. There is acute hæmorrhagic inflammation of the epi- and perineurium of the fifth nerve. The proliferated cells are mostly of the small lymphocyte type mixed with others possessing a larger, clearer nucleus and a fairly large cell-body. In the neighbourhood of the hæmorrhages are many cells with a small deeply stained nucleus and a large cell body filled with refractile purple granules. In the sheath of the Gasserian ganglia there are groups of micro-organisms, and here the perineuritis is very acute, the cell exudate showing various stages of reaction from the small round cell to the typical polyblast (fig. 24). Within the ganglia the reaction is less acute: the connective tissues and adventitial sheaths are proliferating. There is marked chromatolysis of the nerve-cells with homogeneous atrophy of the nucleus, and their capsular nuclei are greatly increased in number. In the pia-arachnoid of the pons there is a considerable degree of round-cell infiltration. Within the pons the vessels are dilated, while the walls of the veins and capillaries show signs of reaction. Chromatolysis is present in the nerve-cells; many of the neuroglial elements have undergone an acute reaction.

(3) *Juvenile general paralysis with bed-sores* over the sacrum, right

hip, and elbow; of three weeks' duration; there was necrosis of the gluteal muscles. At *post-mortem* examination there was great excess of cerebrospinal fluid. There was a purulent inflammation of the epidural tissue over the lowest portion of the cord. Microscopically the loose areolar tissue covering the dura contains micro-organisms, hæmorrhage, and the proliferated cells of the connective tissue. Some of the cells in the exudate resemble polyblasts, in others the nucleus is more deeply stained, and the surrounding protoplasm greater in quantity. Small, round, lymphocytic cells are also present. There are no organisms within the dura mater, but a considerable degree of inflammatory reaction. There is active proliferation of the cells in the perineural sheath of the spinal roots. Here are groups of cells resembling the pseudoplasma-cells of Pappadia. Within the nerves and sensory ganglia there is less reaction. The adventitial cells of the venules and capillaries have proliferated, and plasma-cells are present. The nerve-cells show chromatolysis, and their capsular cells are increased in number. The pia-arachnoid over the lumbo-sacral region is infiltrated

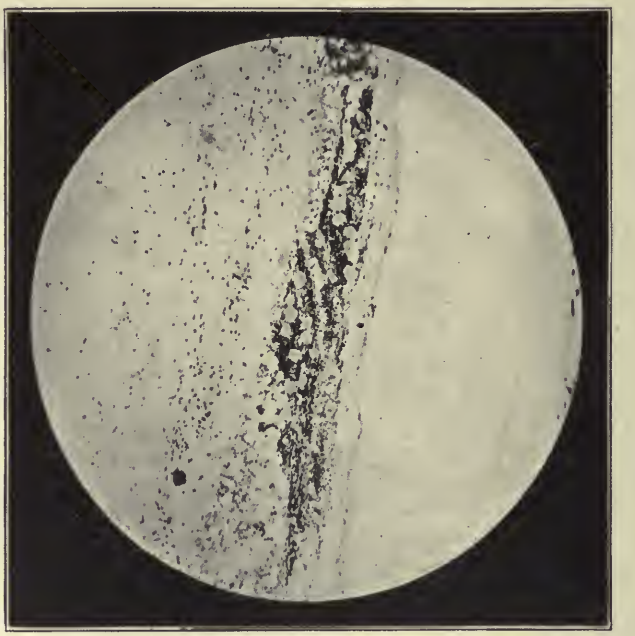

FIG. 24.—From a case of erysipelas of the face. Note the intense inflammatory reaction in the areolar tissue covering the sheath of the Gasserian ganglion.

with small round cells. Within the cord there is proliferation of the adventitial sheath of the vessels, and neuroglia reaction. All the signs of irritation diminished from below upwards.

(4) *Tubercular nodules in pleura.*—The nodules were present on both parietal and visceral pleuræ, on the pleural surface of the diaphragm, and outer layer of the pericardium. The composition of a nodule was fibrous tissue, lymphocytes, connective tissue cells with large clear nuclei, and giant cells. No bacilli were seen by the Ziehl-Nielson stain.

In the *dorsal cord* the endothelial nuclei on the inner surface of the dura are proliferated. The perineurium of the spinal roots and the septa are infiltrated with many lymphocytes and a few plasma-cells. The neurilemma cells are proliferated. The reaction is most marked where the nerves pierce the dura mater. The pia-arachnoid is filled with lymphocytes mixed with plasma-cells. Within the adventitial spaces of the vessels are many lymphocytes and some plasma-cells. Giant cells are present in the pia-arachnoid.

Within the cord the adventitial sheaths are infiltrated with lymphocytes, and cells with a large clear nucleus; plasma-cells occur occasionally near the cord margin. There is a considerable degree of neuroglia proliferation, and by Marchi's method much myelin degeneration scattered uniformly throughout.

In the *cervical region* there is a marked diminution in the degree of inflammatory reaction. The presence of giant cells in the pia-arachnoid is noteworthy. In the *lumbar cord* the adventitia of the vessels in the spinal roots is infiltrated with lymphocytes; these are also present in the pia-arachnoid, and giant cells are to be seen here in the vessel adventitia. Within the cord there are some lymphocytes in the external coat of the larger vessels, the endothelium of the capillaries shows proliferative changes, and the neuroglia cells are increased in number.

(5) *Tubercular lumbar abscess.*—The patient developed symptoms of acute meningitis two days before death. There are tubercle bacilli and giant cells in the wall of the abscess. In the *lumbar cord* the spinal roots are practically normal. The pia mater and adventitial spaces are infiltrated with lymphocytes: a few plasma-cells are present. Some giant cells are to be seen in the perivascular tissue. A mild degree of adventitial proliferation and neuroglia reaction is present within the cord.

In the *dorsal cord* the perineurium of the spinal roots shows a high degree of inflammatory reaction consisting of lymphocytes, proliferated connective tissue cells, and plasma-cells. Rows of lymphocytes occur in the septa between the nerve-bundles. The neurilemma nuclei are increased in number, while the vessels are engorged and dilated. There is much proliferation of the cells of the pia-arachnoid, and its spaces are infiltrated with lymphocytes, as is the adventitia of its vessels. Plasma-cells also are present, and giant cells. Within the cord there are inflammatory changes in the septa and proliferative changes in the adventitia, which is filled with lymphocytes. There are hæmorrhages in the white matter, and in the fourth dorsal segment in Burdach's column near the cord periphery there is a small isolated patch of myelitic softening. The neuroglia is proliferated. Marchi's method shows diffuse myelin degeneration more prominent round the cord periphery. Myelin degeneration is also present in the spinal roots.

In the *cervical cord* the inflammatory reaction in the pia-arachnoid is quite well marked, but of less degree than in the dorsal region. Giant cells are present in the vessel adventitia. The perineurium of the spinal roots shows the same type of reaction as in those of the dorsal cord.

(6) *Cancer of œsophagus* at the level of the crossing of the left bronchus. The tumour was epitheliomatous and was ulcerated. In the *cervical cord* the epidural tissue is greatly inflamed. There are hæmorrhages, micrococci arranged in pairs or short chains, and many degenerated cells—in all probability polymorphs. In the dural tissue are cocci, polymorphs, and some mast-cells. The perineurium of the spinal roots is infiltrated with small round cells; these are also present in the septa between the nerve-bundles, and in one anterior root there are cocci similar to those in the dura lying amongst the reaction cells. The neurilemma nuclei are proliferated, as are the capsular cells surrounding the posterior root ganglion nerve-cells. These show acute chromatolysis and are almost devoid of chromophile material. There are small groups of cocci in the pia-arachnoid, and many degenerate polymorphs, lymphocytes, and proliferated connective tissue cells. Within the cord the vessel adventitia is greatly proliferated; lymphocytes are few in number, and there are no plasma-cells. The neuroglia shows signs of reaction; the nucleus is swollen, rich in chromatin, while the enlarged cell body is branched.

In the *dorsal cord* the dura mater is normal. The pia-arachnoid is infiltrated with many polymorphs and to a less degree with lymphocytes. The perineural sheath of the spinal roots contains many polymorphs; the connective tissue cells and adventitial elements are proliferated; the vessels are dilated and congested; the neurilemma is normal. Within the cord there is a high degree of adventitial proliferation mixed with small, round, lymphocyte-like cells. The endothelial cells of the capillaries are swollen and proliferated. Small hæmorrhages are frequently seen, and the neuroglia cells especially at the cord margin are of the proliferated "amœboid" type.

In the *lumbar region* there are many polymorphs in the pia-arachnoid ; lymphocytes are present in somewhat fewer numbers. Here the vessels are engorged, and also in the spinal roots, whose fibrous sheaths are filled with both polymorphonuclear leucocytes and lymphocytes. In both pia and spinal roots there is a moderate degree of adventitial proliferation; the neurilemma is normal. Within the cord the vessels are engorged, and a very few lymphocytes are present in the adventitial spaces. There are small hæmorrhages in the grey matter.

In the *medulla, pons, cerebellum* and *cerebrum* there are inflammatory phenomena similar to those described above.

(7) *General paralysis of the insane with empyema of right pleural cavity and herpes zoster on the same side.*—The fourth, fifth and sixth right intercostal nerves were examined. The inflammatory exudate in the epineurium shows the same distribution as has been noted in nerves infected experimentally. Its character is subacute and consists in lymphocytes, plasma-cells, fibroblasts, and mast-cells. The cells of the trabeculæ between the nerve-bundles are proliferated. The large majority of the plasma-cells are degenerate, and many resemble compound granular corpuscles. Many of the mast-cells are similar in appearance to the so-called clasmatocytes of Ranvier. The adventitial elements of the veins and capillaries are proliferated and many plasma-cells are present in the spaces.

The connective tissue of the perineurium and its septa has proliferated to form fibroblasts. There is adventitial proliferation in the veins and capillaries. The neurilemma nuclei are swollen, round and pale, while the protoplasm contains numerous lilac-coloured granules (Reich's corpuscles).

Within the right fourth dorsal posterior root ganglion there is a sclerotic area surrounded by a zone of small round-celled infiltration. A similar type of exudation is present in the layers of the ganglion capsule and around its vessels. Two-thirds of the medullated fibres of the corresponding posterior root are degenerated and the neurilemma nuclei proliferated. The cord was examined by Marchi's method and in the fourth dorsal segment there was degeneration in the root entry zone.

The degeneration of this root was traced as far as the third cervical segment.

All these cases except the last one show a diffuse meningo-myelitis of the cerebrospinal axis, the result of toxi-infection of the peripheral nerves. The inflammatory phenomena in the cord and its membranes vary in intensity from case to case according to the potency of the infective agent, and the spread of the inflammation is by the direct continuity so typical of lymphogenous infection. The cases show that any portion of the central nervous system may be attacked by organisms or toxins passing up the nerves from infective foci, and although the morphological changes may vary according to the potency of the exciting cause the anatomical path of entrance and spread is a constant one.

We have already demonstrated how in experimental infection of the lymph-stream of nerves certain structures invariably show the greatest degree of reaction, and the above clinical cases confirm this. These structures are the loose areolar tissue covering the nerve-sheath and the dura mater, and the adventitia of the veins and capillaries. In both the peripheral nerves and cerebrospinal axis the degree of reaction diminishes from without inwards and that portion of the latter directly connected by nerves with the peripheral source of infection exhibits the highest degree of inflammation.

So far we have dealt only with lymphogenous infection of the cord and brain. We shall now contrast the lesions produced by this mechanism with those which occur when a hæmatogenous intoxication is induced.

We have lately undertaken a series of experiments in which the abdominal cavity was chosen as the site for infection. This was done for three reasons: (1) The peritoneal cavity is most suitable for an experiment in which one wishes to avoid infection of the lymph system of spinal nerves; (2) to reproduce as closely as possible a gastro-intestinal intoxication, and observe the effects upon the spinal cord; (3) to ascertain in how far such toxi-infection affected the sympathetic ganglion chain. Celloidin capsules containing a broth culture of the *Staphylococcus pyogenes aureus* were therefore placed in various regions of the abdomen where they became attached to the mesentery, kidney, bladder, or lower border of the stomach. The number of capsules introduced varied from two to six, and the animals were permitted to live for from three to six weeks. Ten rabbits were used and one dog.

At *post-mortem* examination the capsules were found surrounded by an inflammatory exudate, and the vessels of the mesentery, stomach, small and large intestines were much engorged. The inflammatory reaction extended from the neighbourhood of the capsules a considerable distance along the mesentery, and there was abundant microscopical evidence of reaction in connexion with the sympathetic ganglia. Some of these were surrounded by masses of degenerate polymorphonuclear cells, by cells of the lymphocyte type, and by fibroblasts; the vessels passing into the ganglion substance showed proliferative changes in the adventitia. There was chromatolysis of the ganglion nerve-cells, which was central in type, with displacement of the nucleus to the periphery.

The spinal cords were fixed in formalin and bichromate of potassium, and pieces from all regions were cut in longitudinal and transverse section. There was no evidence of lymphogenous invasion either in the sheath of the spinal ganglia, the perineurium of the spinal roots, or in either the dura mater or pia-arachnoid. The posterior root ganglion cells were normal but their capsular cells showed a slight degree of proliferative change.

Within the cord the picture was remarkably different, a most striking feature being the proliferation of the glial elements, which affected both grey and white matter, but especially the outer layers of the latter. The hypertrophied cells were of the amœboid type and frequently formed a row of elements lying end to end. No karyokinetic figures were seen. Some glial elements had undergone regressive change in which the cytoplasm assumed the reticular appearance of a compound granular corpuscle. Many amœboid neuroglia cells clustered thickly round the veins and capillaries of the white matter; while the signs of morbid change in the adventitia and intima consisted only in a slight degree of deformity of the nuclei. This contrasts sharply with lymphogenous inflammation where adventitial proliferation is constant. In addition to this generalized neuroglia reaction there were small scattered sclerotic foci consisting of glial elements in the resting stage following proliferation. Their nuclei were smaller than normal, filled with chromatin, and their cell bodies and processes massed together to form a syncytium. They occurred most frequently in the neighbourhood of the cord margin, and at times were definitely related to dilated vessels and hæmorrhages. Numbers of cells of the lymphocyte type were seen in both grey and white matter in some of the experiments.

The nerve-cells showed early chromatolysis. In some the nucleus was rather diffusely stained, an appearance suggestive of the initial stage of homogeneous atrophy, and the chromophile elements in the cell centre had an increased affinity for the stain, while their edges were not so sharply outlined as in the normal. In other cells the elements at the edge of the cell body were disintegrated. There were many cells of the lymphocyte type scattered amongst the nerve-cells and often lying in close proximity to them. Many swollen neuroglia nuclei were found round the margin of the nerve-cells.

Portions from the cervical, dorsal and lumbar levels of the cord were examined for alterations in the myelin sheath. The Marchi, Wolters, and Donaggio methods were employed, and all gave positive results. The latter method was found to be the most trustworthy for demonstrating the early changes in the myelin sheath. The striking feature of the medullated fibre lesions was their non-systemic character. The two areas involved were the cord periphery and the posterior columns. In the cervical and lumbar regions the whole cord periphery was affected, leaving the pyramidal tracts and antero-lateral basis bundles free. In the dorsal cord this marginal degeneration did not involve the posterior columns. The degeneration of the posterior columns varied from region to region. In the lumbar cord it formed a small triangle round the posterior end of the postero-median septum with its base towards the cord margin. Higher up, in the dorsal cord, the degenerated fibres formed a V whose apex reached the middle of the septum, while its limbs diverged backwards towards the cord margin, leaving the area round the posterior third of the septum practically free from degenerated fibres. In the cervical cord the degenerated fibres were more numerous than in the lower regions and formed a narrow column situated slightly external to each side of the median septum and running backwards to join the marginal degeneration. The medullated fibre lesion was therefore maximal in the cervical and minimal in the lumbar region, and the root entry zones throughout the cord were free from degeneration.

Wolters' method showed no sclerosis in any of the tracts; but in the external portions of the cord the medullated fibres were swollen, irregular, and often fragmented, appearances resembling those found in the cord œdema of cancer cachexia and pernicious anæmia. By Marchi's osmic acid method some fibres scattered throughout all regions of the cord gave a positive reaction. In the vein of the postero-median septum the adventitial sheath sometimes contained a considerable quantity of degenerated myelin which had evidently been carried there by the lymph current.

The changes in connection with the vessels varied very considerably and were more evident when four or six capsules were placed in the abdomen. In some experiments nothing beyond an increased affinity for aniline dyes on the part of the adventitial nuclei, and some distortion of the intimal nuclei of the veins and capillaries was noticed. There were a few cells of the lymphocyte type in the adventitial lymph spaces. Where a higher degree of toxicity was induced the changes in the vessels were the most prominent feature. All the arteries, veins, and capillaries in both grey and white matter showed hyaline degeneration of their walls, and many contained partial or complete thrombi. In the vessels showing incomplete thrombosis the hyaline material lay along the vessel wall as a thick band connected by trabeculæ with a very definite hyaline network in the lumen. Many vacuoles were seen in the thrombi, and there was practically no disturbance of the intimal or adventitial nuclei. Morbid changes of somewhat the same nature have been observed by ourselves and Ziveri in senile dementia [45], by Campbell in general paralysis of the insane [7], and by Alzheimer [4] in general paralysis of the insane and epilepsy.

If we summarize the changes above described, we find (1) the most highly developed structures, the nerve cells, suffer least of all; (2) there is primary degeneration of the myelin sheath round the cord margin and along the postero-median septum; (3) the myelin degeneration is greatest in the upper part of the cord; (4) there is œdema of the cord; (5) there is active proliferation of the perivascular neuroglia; (6) the vessels are dilated, congested, are hyaline, and contain thrombi of the same nature. If these be now contrasted with the cord lesions in lymphogenous infection the difference is at once obvious. Lymphogenous infection is characterized by (1) the reaction of the cells of the fixed connective tissue; (2) the proliferation of the cells of the adventitial sheath of the veins and capillaries; (3) the appearance of numerous scavenger-cells when the myelin is disintegrated; (4) nerve-cell degeneration and neuronophagy. From the above one must conclude that the lesions in hæmatogenous intoxication are of a degenerative nature and differ very widely from those found in lymphogenous infection, where the fixed tissues are actively proliferating and all the morbid phenomena are of an inflammatory type. The difference between the two might, therefore, be expressed by saying that in lymphogenous infection the inflammatory phenomena reach their maximum; in hæmatogenous intoxication they are reduced to a minimum.

In giving a short preliminary account of these experimental hæmatogenous lesions, we feel that the term "hæmatogenous" requires qualification. We do not consider that the term sufficiently explains the mechanism of production. It would seem as though there was another factor at work. If we look at the distribution of the myelin degeneration alone for a moment, round the cord margin where œdema is present, and on either side of the postero-median septum, the explanation of a "general intoxication" is hardly sufficient. Weaker resistance on the part of the fibres in those situations might be put forward as a predisposing cause, but this suggestion cannot be substantiated.

Lesions of practically the same distribution are found in cancer cachexia, pernicious anæmia, Addison's disease, &c. It is of importance to note that the grey matter of the cord so richly supplied by the anterior spinal artery may be normal; Goll's tract in the cervical enlargement is attacked in its middle third, leaving the long lumbosacral fibres so far away from their trophic centre untouched; between the lesions in the cervical, dorsal, and lumbar cord there are great differences not to be accounted for by a focal lesion. Such a distribution of degeneration cannot be explained by a general intoxication. It fails completely when we consider that the areas supplied by the pial vessels, the cord margin and postero-median septum, show degenerative change, while the regions supplied by the anterior spinal arteries escape. It is highly probable that there must be another factor besides intoxication which determines the localization of the degenerations, and certain indications point to the sympathetic nervous system.

We have shown evidence of involvement of this mechanism in the inflammation round the sympathetic ganglia, the proliferative changes in the adventitia of their vessels, and in the chromatolysis of the nerve-cells; and when it is remembered that the cord lesion in abdominal cancer and Addison's disease—in both of which sympathetic reflex action must be considerably disturbed—have almost the same distribution as in our experiments, sympathetic influence cannot be excluded.

There is evidence in the vessels of the cord, too, of altered sympathetic action; in the dilatation, hæmorrhages with sclerosis, and in the hyaline thrombosis—all pointing to stasis. As to whether this stasis is due to toxic action upon the prevertebral chain or is caused by the direct action upon the cord vessels of a toxin in the general circulation, it is difficult to say. This latter suggestion seems improbable, as judging from the relative integrity of the nerve-cells and the minimal reaction of the vessel endothelium within the cord, the toxicity of the blood-stream must have been very mild. In all probability both factors come into play. The disturbance of the sympathetic influence upon the cord vessels might be held responsible for a dilatation and increased permeability of their walls, so facilitating the passage of toxins into the surrounding tissues. Evidence of this is seen in the proliferation of the perivascular neuroglia. It is conceivable, however, that with time a permanent paresis of the vessel wall with slowing of the blood-current occurs, thus affording the most favourable conditions under which mild toxicity of the blood could exercise a deleterious action upon the vessel walls and nutrition of the nervous tissues generally. Whether we are right or not in attributing importance to the sympathetic factor must be left to further experiment. Our present position with regard to these hæmatogenous lesions is that the term "general intoxication" expresses their pathology inadequately.

From the above clinical and experimental study it is clear that the two mechanisms of infection of the cerebrospinal system—the hæmatogenous and lymphogenous—are characterized by sufficiently distinct morbid phenomena, and if we apply the results of the experiments to the human subject we obtain very considerable assistance in arriving at an understanding of the genesis of certain lesions.

We have brought forward ample evidence to show that acute and chronic myelitic conditions are readily produced by infection of the ascending lymph system in nerves. We have previously given it as our opinion that general paralysis of the insane is a chronic inflammatory disease of lymphogenous origin. This opinion is based on the close similarity between the vascular lesions in this condition and those found in our experiments where the lymph system of the nerves or cord is infected. The striking predominance of adventitial proliferation and infiltration can be explained only by toxi-infection of the cerebrospinal lymph. There is no evidence of a general blood intoxication, for in dementia paralytica, as in our experiments, the endothelium of the vessels may be quite unaffected, while the adventitial spaces are packed with the products of proliferation (fig. 25). Further, to tabes dorsalis we assign the same lymphogenous genesis. The vascular phenomena, similar to those in general paralysis, the constant primary affection of the root entry zones, and the rigidly systemic character of the lesion preclude any other conclusion.

We have shown that certain cases of acute meningo-myelitis fall into the lymphogenous category, and there is now a preponderance of evidence to show that acute poliomyelitis must also be included in this group. The whole picture of this disease is one of a disseminated meningo-myelitis, and as the brain may be affected in adults especially, the more comprehensive term of disseminated meningo-myelo-encephalitis has been suggested by Wickmann [43]. There are many facts which show that infantile paralysis cannot be a blood infection, and indisputable evidence in favour of the lymphogenous genesis. This latter view is upheld on clinical and experimental grounds by both Wickmann [43] and Römer [37], and with them we agree. The localization and morphology of the lesions and the continuity of extension are characteristic of lymphogenous infections, a continuity which varies naturally, and attains its maximum in the acute ascending paralysis of Landry.

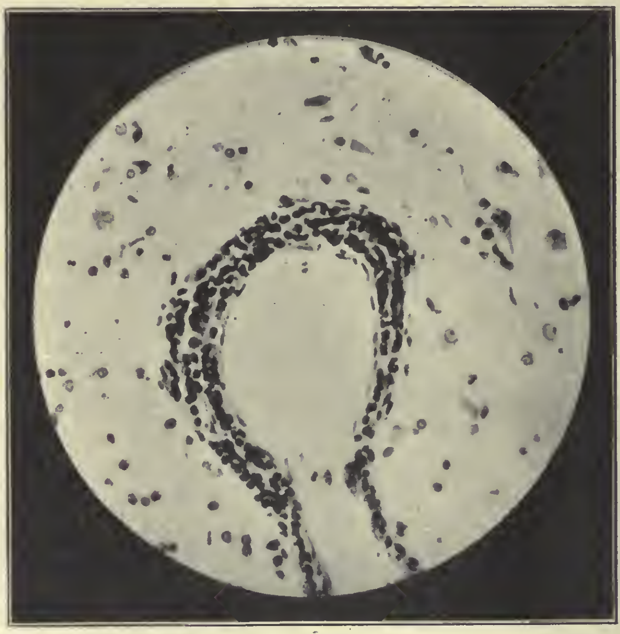

FIG. 25.—Venule from the cortex of a case of general paralysis of the insane. Note the high degree of adventitial proliferation ; the intima is normal.

There is one important feature in connexion with the question of lymphogenous propagation and extension to which Homén [13] has drawn attention—viz., that the posterior root ganglia act as traps or filters, and form a kind of barrier against the further centripetal passage of organisms. This observation, although difficult to explain at present, would seem to be of special significance, as in all our experiments dealing with lymphogenous infection we have found a large collection of reaction cells and hæmorrhage at the proximal pole of the ganglion. It may be that this special reaction indicates the existence of some defence mechanism against the further central extension of toxi-infection, and that an additional factor is introduced by a local anatomical structure. It is of interest to note in this connexion that an analogous though more intense lesion is found in the ganglion in herpes zoster, and we would suggest that this disease also falls into the lymphogenous group, for we have observed the typical clinical appearances and pathological lesions of zoster to follow an empyema accompanied by ascending inflammation of the intercostal nerves. It is not improbable, therefore, that Homén [13] is quite correct in calling the root ganglion a trap for noxious agents ascending in the lymph-stream of nerves; and if we accept that it is a defence mechanism, and herpes zoster an expression of arrested ascending lymphogenous infection, then the suggestion might be put forward that the exciting agent which is not trapped passes onwards to the spinal cord and causes meningo-myelitis in some form or other.

A consideration of the phenomena in the subacute non-systemic lesions of the cord such as occur with or without anæmia, Addison's disease, cancer cachexia, &c., shows that they must be included in the hæmatogenous category. There is an entire absence of the proliferative change in the adventitia of the veins and capillaries which characterizes the lymphogenous infections. The root entry zones in the posterior columns are, except perhaps in the latest stages of the affection, quite sound, while there is a marked sclerosis around the postero-median septum. The nerve-cells in the grey matter maintain their integrity. The morbid picture is degenerative, not inflammatory; in type and in the zones affected it corresponds with what is found in experimental hæmatogenous intoxication.

In describing the lesions produced in our experiments we have indicated that the cellular elements present in the inflammatory reactions have, under varying conditions, exhibited markedly different characteristics. On the other hand we have found that where the conditions have been as nearly identical as possible similar appearances have been produced. If the extremes in the series—the swollen nuclei and the plasma-cells in the walls of the veins and capillaries in the sub-acute cases, and the accumulations of cells indicative of an acute lesion or of destruction of nerve tissues in the other cases—had alone been considered, we might have been led to describe these conditions as distinct classes or varieties of reaction; but, seeing that it has been possible to observe a series of intermediate stages, extending from one extreme to the other, such a division was evidently not justifiable. Hitherto such an arbitrary separation has been attempted under the terms hæmorrhagic, interstitial, and parenchymatous inflammation. Possibly from the point of view of the clinician this division was of use, and especially so seeing that the pathology of inflammatory processes in the nervous system was not established on a scientific basis. But since the pathology of these conditions and the mechanism of their production have been more thoroughly investigated such a classification can no longer be admitted. Still, although so much work has been done and many valuable data have been collected, the results have been somewhat contradictory and a certain amount of confusion exists even now. It has been shown, however, by the investigations into the characters, the origin, and the significance of the various types of cells, that inflammatory processes in the nervous system must be considered as a whole; and only by considering the etiology and the mechanism of production of these processes together with the results revealed by the microscope will it be possible to explain the various morbid conditions.

The experiments which we have carried out may be divided into two classes, viz., firstly, those in which there was no escape of organisms from the capsule and in which, therefore, the results must be regarded as the effect of the action of a toxin on the tissues; and secondly, those in which the capsule had leaked or in some cases burst and there followed a growth of organisms outside which produced a much more intense reaction. But although we have divided the experiments into these two classes we hope to show that the differences in the results are more a matter of degree than of kind.

In the series in which there had been no escape of organisms from the capsules, the chief type of reaction cell present was the plasma-cell. Attention has been directed to the characters and origin of these cells since the appearance of Unna's work on their existence in granulation tumours of the skin and more especially since the work of Marschalkó [20] in 1895. Unna [41] based his definition of these cells on their staining properties, Marschalkó [20] relied on their morphological characters. But while the description of Marschalkó for the fully developed cells is still retained it has become recognized that their form and staining capacity may vary considerably under different conditions. Nissl [24], referring to the early stages of the overgrowth of the tissues of the walls of the vessels, said that "quite small forms of plasma-cells may be seen with a small cell body which stains much more deeply than is usual in these cells." Degenerative phases also have been described. In this phase they sometimes resemble reticulate cells (Unna [41]), or they may be vacuolated, or they may show solution (Herbert) or hyaline degeneration of their protoplasm (Joannovics [16]); some authorities have seem them loaded with pigment. The recognition of these forms is important and materially assists in the task of determining the origin of these cells and their relation to the cells amongst which they are found.

The question of the origin of plasma-cells has given rise to endless discussion. Unna [41] considered that they were derived from connective tissue cells; Marschalkó [20], on the other hand, traced them from the lymphocytes of the blood, and chiefly from the veins. This view was held for a long time and has been strongly supported by Nissl [24]. Nissl has stated that he is firmly convinced that plasma-cells are exclusively of hæmatogenous origin, and that all the stages between the lymphocyte within the blood-vessels and the plasma-cells in the sheath of the vessels can be traced. But when speaking of their appearance in granulation tissue he admitted that intermediate forms between Unna's plasma-cells and connective tissue cells, and also between Unna's plasma-cells and lymphocyte-like elements, existed. In another paragraph he stated that Marschalkó had observed cells with morphological characters similar to those of his plasma-cells in inflammatory granulation tumours and that they were sharply distinguished from lymphocytes and other cells with basophile bodies; but he added, "the typical Marschalkó plasma-cell is not so absolutely distinctive that it can under all conditions be separated from the lymphocyte-like elements and connective tissue cells with basophile cell-body, and, further, intermediate stages occur between those forms of cells." Observations similar to these have led many investigators to speak of two varieties of plasma-cells: those of Unna—histogenous—and those of Marschalkó—hæmatogenous. Joannovics [16], in a paper published some years ago, said that plasma-cells, besides finding their origin from lymphocytes of the blood, could be derived also from the cells of connective tissue under certain conditions. In a more recent paper he recognized a histogenous origin only and brought forward, amongst other evidence, the following reasons against the hæmatogenous theory: (1) Inflammatory tissues are invaded by leucocytes, but there is no increase of intravascular lymphocytes. (2) Schridde and he claim to have followed plasma-cells from the tissues into the blood-stream during digestion. (3) The presence of plasma-cells in normal tissues, when no relationship to lymphocytes can be traced, makes it difficult to admit their origin from the blood elements. Marchand also considered that certain adventitial cells possess the capacity of forming elements having the characters of lymphocytes and large mononuclear leucocytes, and he applied the term "lymphocytoid" to the cells formed outside the blood-stream; amongst them he included plasma-cells. The separation of the tissue lymphocytes from the hæmatogenous lymphocytes has been strongly supported by Pappenheim, who held the former to be the mother-cells of the plasma-cells. These tissue lymphocytes are now regarded as histogenous elements which have sprung from sessile perivascular cells, normal constituents in the walls of the vessels, under the influence of physiological and pathological stimuli, and from these tissue lymphocytes the plasma-cells are developed. Schmauss [38] also has spoken of the usually sessile elements of the vessels becoming wandering cells under suitable stimulation.

In our experiments the toxin derived from the capsule containing the organisms produced a reaction in the various tissues along the path by which it advanced towards the central nervous system. In the cases in which the capsule had not burst and there was no growth of organisms in the tissues, this reaction was most marked in the adventitial sheath of the veins and capillaries: the cells of this sheath were undergoing a very active proliferation and, as a result, collections of cells of various forms appeared. Most of the cells had a rounded shape; the nucleus was round or oval; it stained deeply and uniformly in some and in others the chromatin was arranged around the nuclear membrane. The quantity and the disposition of the protoplasm varied also. In some cases there was no protoplasm to be seen; in others a very thin layer surrounded the nucleus; in some, again, the protoplasm was separated from the nucleus by a clear space. Another phase was indicated in cells whose nucleus had become excentric with a clear space on its central side bounded peripherally by a layer of vaguely granular protoplasm. This series of cells demonstrates the intermediate stages in the development of the typical plasma-cell from the rounded elements occurring amongst the proliferated cells of the adventitial sheath. In some areas the endothelial cells of the small veins and of the capillaries were swollen and irregular in shape; they projected into the lumen and, in some instances, were detached and lay free in it. In connexion with this it is interesting to point out that Beattie [5] has described a swelling of the intimal cells and their complete detachment from the walls of the vessels in omental inflammation. Adami [1] also has said that "the evidence accumulating of late years appears to point in one direction, namely, that the mononuclear cells seen within the vessels during the process of inflammation are of endothelial origin." Occasionally, in our experiments we have found many of these cells in veins partially thrombosed, but at the same time there was no special collection of them in the adventitial sheaths and they were not seen passing through the walls of the vessels. That thrombi can be formed in the vessels during the early stages of similar inflammatory processes has been demonstrated by Righetti [36] after injection of diphtheria toxin into the sub-dural space. It will be necessary, therefore, to bear these conditions in mind when discussing the origin of plasma-cells from mononucleated cells within the vessels. In the small veins and capillaries further from the source of the irritant, for example, in those situated near the central canal of the spinal cord, the sole reaction present was a slight swelling of the nuclei and an increased staining capacity of the cells of the intima.

But, besides the cells of the adventitial sheath, those of other tissues were reacting, especially at the level of the seat of the capsule. The cells of the epi- and perineurium in Series I, and of the dura mater and of the areolar tissue outside it in Series II, were proliferating, and in the collections of cells thus produced definite plasma-cells and also examples of the intermediate forms referred to were numerous. The nuclei and cell-body of these plasma-cells in the dense tissues were narrow and elongated, and the latter stained deeply with the toluidin and pyronin-methyl-green methods; the intermediate forms were shown by the nuclei becoming more rounded and by a halo appearing on one side of it. In the loose areolar tissue various forms from the small round nucleus to the typical plasma-cell lay along the trabeculæ.

The evidence derived from these experiments, therefore, suggests that plasma-cells may spring from the cells of the connective tissues as well as from the adventitial sheath of the vessels. Catòla [8] has found plasma-cells in the liver in cases of general paralysis, not around the vessels but amongst the cells of the perilobular connective tissue and around the biliary canals—in fact, in regions where the connective tissue was proliferating. The fusiform cells of this tissue were described as being strongly basophile: their protoplasm increased gradually in quantity and they assumed the morphological characters of plasma-cells. A similar appearance of these cells derived from connective tissue has been demonstrated by Pappadia [33] in the wall of a cysticercus cyst in the brain. Here, also, the fusiform fibroblasts swelled up and exhibited a basophile protoplasm; they gradually became polygonal and rounded in the outer layers of the cyst wall and acquired the characters of typical plasma-cells.

The conditions found by these investigators led them to suggest that these cells may spring from the cells of the connective tissues; the results of our experiments and the examination of tissues taken from clinical cases, e.g., the fibrous sheath of a lymphatic gland invaded by a metastatic growth from a malignant tumour of the lower jaw, have demonstrated that in certain instances such an origin must be admitted. At the same time there can be no doubt that in our experiments the great majority of the plasma-cells sprang from the proliferated cells of the adventitial sheath.

In the experiments in which the capsules had burst and the organisms had grown amongst the tissues another type of cell, corresponding to the polyblast of Wickmann, was the most prominent feature in the sections examined. In his cases of acute poliomyelitis, Wickmann [43] found the walls of the vessels occupied by large cells with a rounded or oval nucleus, often indented on one side; the cell-body was sometimes clear, but in many instances it contained a few deeply stained masses irregularly distributed. Frequently, the nucleus was so much indented and its form was so irregular, that it resembled that of a polymorphonuclear leucocyte; the chromatin was collected into a few small granules united by a reticulum. By many observers these cells have been regarded as polymorphonuclear leucocytes, but Wickmann [43] maintains that this view is not correct. Most of the infiltration into the pia mater is undoubtedly of lymphocytic origin, i.e., the cells have sprung from the wandering lymphocytes of the adventitial sheath of the vessels, and Wickmann argued that a similar derivation must be admitted for the cells found in the spinal cord. He recognized many intermediate forms between these cells and the lymphocytes. The following arguments were adduced against the leucocytes being the progenitors of the polyblasts. It was admitted that the nucleus of the polyblast might be so much lobed as to resemble the nucleus of the polymorphonuclear leucocyte, but it possesses granules of chromatin united by a reticulum which is not seen in the leucocyte; and in tissues fixed in alcohol the cell-body of the polyblast is stained by the pyronin-methyl-green method, while that of the leucocyte is not; and by other suitable staining neutrophile granules can be demonstrated in the leucocyte which are absent from the body of the polyblast. Wickmann [43] concluded that, in his cases, the polyblasts sprang from the wandering lymphocyte and that the hæmatogenous leucocyte did not participate in their formation. He admitted that some of the small neuroglia cells offered appearances difficult to distinguish from the polyblasts, but the facts that these cells were found in the pia mater where there are no neuroglial elements, and in the sheaths of the vessels where they were obviously derived from the adventitial cells, are against such an origin. Moreover, in our cases, although a consideration of the small neuroglia cells might leave one in doubt, yet observation of the whole reaction of the neuroglial elements made it certain that the polyblasts did not owe their origin to them.

In our experiments the polyblast type of cell was seen best in the reaction in the pia mater and in the walls of the vessels passing from it into the spinal cord, in those cases in which the capsules had burst and the organisms could be followed along the intercostal nerves to the dura mater. In this region, where it was obvious that the potency and quantity of the irritant was much greater, all the cells of the pia mater and the endothelial and adventitial elements of the vessels were actively proliferating and the cells arising from this reaction were of the polyblast type. But at the site of the capsule which had not leaked some similar cells with pale nuclei, oval in shape, regular in outline, or indented on one side, were present amongst a far greater number of round, darkly stained nuclei and plasma-cells. This was the area of greatest intensity of reaction in this series, but it was not so acute as in the series with the burst capsules. It was easier, therefore, to follow the intermediate stages between the cells of the connective tissues and those of the walls of the vessels and the polyblasts. The polyblast, as well as the plasma-cell, is therefore of histogenous and not of hæmatogenous origin.

But besides the polyblasts in the areas of acute reaction there appeared around the capsule bands of fibroblasts, fusiform cells with an elongated, pale nucleus and a greatly increased quantity of basophile protoplasm which did not generally surround the nucleus but was collected at the poles. In some cells, however, the protoplasm encircled the nucleus, and in others this was placed excentrically. Intermediate forms between the elongated fusiform cells and the rounded cells were evident. These bands of cells in parallel rows were present in all the experiments, but in much greater numbers when the capsule had burst.

With regard to the compound granular corpuscles, Gitterzellen (Nissl [24]), Körnchenzellen (Friedmann [11]), Abraumzellen (Merzbacher), a similar divergence of opinion has existed. Friedmann [11] divided these cells into two groups, granulo-adipose cells and epithelioid cells. The former he derived from white blood corpuscles and the latter from neuroglia chiefly, but also from adventitial cells. Schmaus [38] has admitted a double origin in foci of softening—in the early stages from polymorphonuclear leucocytes; later another type of cell, corresponding to the epithelioid cells, appeared. Of the origin of this type he was uncertain, but he thought they sprang from adventitial and endothelial cells. Merzbacher has called these cells Abraumzellen, indicating their function thereby; he traced them from adventitial cells and from the neuroglia. Nissl [24] has stated that not all the cells which contained fat were compound granular cells and he limited the term to those which acted as phagocytes; these he traced from the adventitial and endothelial cells. Schroeder found these cells in a focus in which there was some destruction of nerve-fibres but no proliferation of the elements of the vessel walls, and he concluded they were derived from the neuroglia cells. Bonfiglio [6], from his experiments, decided they had a dual origin, from the cells of the vessel walls and from the neuroglia.

It will be remembered that in the lateral columns of the spinal cord when the growth of organisms had spread along the intercostal nerves to the dura mater, a considerable collection of cells had appeared which offered some definite peculiarities of structure. The nucleus was deeply stained and often situated at the side of the cell; but the chief peculiarity lay in the formation of a reticulum in the cell-body (fig. 20). In many cells the spaces of this reticulum were unoccupied and gave the appearance of vacuoles, but in others they were filled by a material which was faintly stained. Cells with a reticulum in the cell-body occurred also in the epidural tissue—i.e., in the region of the most intense reaction—in the cases in which the capsules had not burst. Here they were mixed with a large number of polyblasts and plasma-cells, in their adult and intermediate stages, and with a form of cell which has been spoken of by Friedmann [11] as the epithelioid cell. In these situations the appearances suggest that these reticular compound granular cells have sprung from the proliferated elements of the adventitial sheath of the vessels and of the connective tissue cells of the epidural sheath. But in the most recent series of experiments, in which the capsules had been placed in the peritoneal cavity and in which nutritive changes had occurred in the spinal cord, similar cells were met with in close relation with nerve-fibres undergoing degenerative changes. In these cases there was no reaction of the cells of the adventitial sheath, and it was evident the compound granular corpuscles present were derived from the neuroglia cells.

An examination of the results of many investigations regarding the origin of the types of cells referred to in this paper, and of the phenomena observed in the experiments in which we have induced inflammatory processes of varying degrees in the nervous system, provides conclusive evidence that the cells of reaction against an irritant are derived from the cells of the tissues with which the irritant comes into contact; in other words, all these varieties of cells—plasma-cells, polyblasts, fibroblasts, epithelioid cells, and Körnchenzellen—are of histogenous and not of hæmatogenous origin.

The fact that all these forms of cells of reaction have been traced from a common source suggests that there must be some principle underlying these processes which, if discovered, would prove that they are not so independent of each other as they have often been assumed to be, and would clear away much of the confusion at present obscuring the question. One of the chief difficulties has been the insistence on the use of the word "typical." We constantly see reference made to the "typical" plasma-cell, to the "typical" polyblast, or to the "typical" Körnchenzell, and by many the cell which was not a "typical" cell of some sort has been left out of consideration. Bonfiglio [6] criticized the statement of Nissl [24] that too much importance was not to be attached to the presence of intermediate forms. Such a statement might be accepted when dealing with isolated cells, or with cells in small numbers, but when the intermediate forms exist in large numbers they should not be ignored. Another difficulty has been that the investigations have not been carried out on sufficiently broad lines; that which has been simply one stage in a complex inflammatory process has been examined without due attention being given to the conditions under which the process arose and to the earlier stages through which it may have passed. Hints of the necessity of looking beyond the mere type of cell have been made by several observers; for instance, Wickmann [43] has suggested that the nature of the infiltrating cells depends on the irritating agent and not on the localization; and Bonfiglio [6] expressed the opinion that in different pathological conditions these elements may have a varying origin. There can be no doubt that in order to understand the significance of a reaction occurring in the nervous system it is necessary to consider the cause of the inflammatory process, its intensity and the length of time it has acted, together with the morphological form of the cells infiltrating the tissues.

A more comprehensive communication on this subject has been published by Friedmann [11], in which he has given the results of his investigations regarding the reactions which accompanied different degrees of irritation in the nervous system. He started with a simple form of morbid change, viz., hyperæmia, and found that the vessels and the lymph spaces in their sheaths were dilated, and that regressive changes had occurred in the elements forming the vessel walls. When a hæmorrhage had taken place amongst the nerve tissues, a definite reaction followed. The blood soon disappeared, chiefly in the lymph spaces of the vessels in the neighbourhood, and at the edge of the area containing the hæmorrhage a cyst wall had formed, consisting largely in dense connective tissue fibrils, vessels and cells. Outside this, in the tissues limiting the softened area there was a looser cicatricial tissue infiltrated by a large number of Körnchenzellen. In cases of thrombosis or embolism there followed a complete anæmia and an intense œdema in the centre of the focus. In a short time this centre was occupied by the detritus of broken-down nerve-cells and fibres, and in this were many Körnchenzellen. Experiment proved that these cells appeared on the second day and that their numbers increased during the following days. Then later the fibrous organization and sclerosis characteristic of encephalomalacia followed. These were the constant results after simple destruction of nerve tissues by vascular lesions.

Then in his experimental work he showed that slight aseptic wounds of the brain produced a central necrosis immediately surrounded by a necrobiotic area containing many Körnchenzellen and a peripheral zone with round cells, new vessels, and a proliferation of the fixed tissue elements, leading to a sclerosis. With a more intense irritation, such as the application of corroding agents to the brain, the process was more active. At once, around the necrosed, corroded area, there was a condition of irritation of the vessels with hyperæmia, extravasation of blood and emigration of round cells. By the third or fourth day the neuroglia cells were swollen and Körnchenzellen were present; and from the fifth day a breaking down of the nerve tissues was observed and also large collections of epithelioid cells and Körnchenzellen. The vessels were thickened by proliferation of the endothelial cells, new vessels were formed, and organization followed. Here again there was a destruction of nerve tissues, but the cause had acted also as an irritant to the mesodermal tissues.

In still more acute cases, the result of a meningitis or an invasion by the influenza bacillus, the hyperæmia, with or without a softening, was followed by an active proliferation of the fixed tissue elements. From this proliferation there appeared Körnchenzellen and other large, round cells, the epithelioid cells. These last were often not limited to the sheaths of the vessels but infiltrated the tissues, without, however, any real softening being present. Much new vessel formation occurred. The termination of the acute process was either a primary organization and cicatrix—and this was the result in the corroding experiments—or, as happened in the encephalitic cases, the young cells formed a protoplasmic network whose meshes were occupied by round cells, and then later this contracted and formed a cicatrix. In other areas there was a large collection of fibroblasts, or, where a central necrosis had occurred, the usual cyst wall was found. In cases of abscess in the central nervous system there was a migration of leucocytes in the first few hours and the neuroglia cells were swollen. On the third day the nerve tissues were breaking down and Körnchenzellen were as numerous as the leucocytes. By the tenth day the area of infection was surrounded by a membrane consisting in (1) a layer with round cells, new blood-vessels, Körnchenzellen and disintegrating nerve tissue; (2) a layer with many vessels and fibroblasts forming a granulation tissue; (3) a layer in which the nerve tissues, although injured, were still preserved; the walls of the vessels were infiltrated, and the neuroglia cells were reacting. Friedmann [11] from this work arrived at the following conclusions:—

(1) All the different forms of reaction can be produced by the same agent or by any sufficiently strong stimulus, whether it be that which causes a meningitis or whether it be an embolism, an aseptic wound, an exogenous corroding agent or excessive heat.

(2) The whole complex series of changes from the small round cell infiltration, the intense inflammatory reaction with the giant cells and large cell proliferation, to the softening with "Körnchenzellen," may be present in one and the same case.

(3) The more intense inflammations progress by steps, and these steps correspond to those pictures of the morbid process which we have

been accustomed to regard as separate forms of encephalitis, hæmorrhagic, parenchymatous or hyperplastic.

This work is of the greatest importance in that it shows that although the inflammatory process under different conditions is exceedingly complex, there are certain principles underlying it which enable us to recognize in it different degrees of one process rather than several independent series of reactions. It demonstrates that not the particular kind of cause, but its intensity and the length of time it acts on the tissues, are the essential factors in determining the results. The initial stage may be a gross destruction of nerve tissue, and this will be followed by a reaction whose function it is to remove the débris, as in a case of hæmorrhage, thrombosis, or embolism; or it may combine a condition of irritation of the mesodermal tissues simultaneously with that of destruction, as in the action of corroding agents; or it may exhibit at first the phenomena of irritation induced by bacilli or their toxins, and the destruction of the nerve tissues will occur later. And, as Friedmann [11] has shown, the character of the reaction will change from day to day in the course of the process, especially when the irritation is the first result and the destruction follows.

Now, although the initial stages may vary so much, the final stage, following the destruction of the nerve tissues, presents fairly uniform characters; but here also the question of degree again arises. The necessity of separating these final from the earlier stages has been pointed out by Schmaus [38]. He admitted the continuity of the stages in the inflammatory processes occurring in the nervous system, but indicated that not all are the direct result of the action of the irritant. In some acute processes, where the irritant acts for a short time only, a slight parenchymatous degeneration is produced and the products of this degeneration may be disposed of by a reaction of the neuroglia without any infiltration of the tissues. But, if the breaking down of the tissues is more extensive, it is found that the reaction is more complicated. Besides the neuroglial overgrowth there is a large collection of phagocytic wandering cells. Again, the inflammatory process may be so acute that it affects not only the nerve-cells and fibres, but leads to a softening of all the tissues in the area attacked. This, at first sight, offers a very different picture to that which characterizes an ordinary simple softening. It is generally considered that a simple softening is distinguished by the presence of detritus and Körnchenzellen; but if the area of softening produced by an embolism be examined within a few hours of the blockage of the vessel, it will be found that there is a swelling of the tissues, and the process goes on to the breaking down of the various elements; it is a liquefactive process, but it is also inflammatory, because it is accompanied by an emigration of leucocytes; only later do the larger phagocytic elements appear. In what is called an inflammatory softening the tissues become infiltrated with leucocytes, then break down, i.e., liquefy, and there remains a collection of degenerated tissue to be removed. Now the removal of this débris is accomplished by cells similar to those which act as phagocytes in the case of a simple softening, viz., by Körnchenzellen. But these cells are not the direct product of the action of the disease-producing agent, they are called forth by the presence of the débris of the tissue destroyed by the noxious agent. The Körnchenzellen are the type of cell which removes the products of degeneration, and they are recognized as the phagocytes of the central nervous system. Therefore, whatever may be the cause, the characters of the softening are fairly uniform, and are to be distinguished from those of the primary reaction which is the direct result of the action of the irritating agent. Schmaus [38] recognized, however, that there is no line of demarcation to be drawn between the two; the elements of the secondary process are intimately mixed with those of the primary reaction. Theoretically, the phases of absorption and organization may be sharply separated from the primary reaction, which includes the circulatory, regressive and progressive changes described by Schmaus [38] and others, but practically it is found that the elements capable of removing the débris are present at the same time as those of the primary reaction. Schmaus [38] stated that the separation offers least difficulty in the case of ischæmic degeneration of the nerve tissues following ligature of the aorta, but it is not possible in more chronic conditions. In the simultaneous degeneration of the parenchyma, the infiltration with wandering cells, and the overgrowth of the neuroglia, we see a temporary phase of a process which can end in sclerosis, but which during its course will present all the stages of inflammation. Besides, in toxi-infective myelitis the degeneration of the parenchyma may be the result of the action of the disease-producing agent, which is responsible also for the vessel changes, the exudation, the infiltration, and neuroglial overgrowth; or the infiltration and neuroglial overgrowth may be called forth by the presence of degenerated nerve tissues. Further, the thrombosis and embolism with the accompanying lymph stasis may be the direct result of the inflammatory irritant. In all these cases the different causes and signs of reaction will be so interwoven that it will be impossible to separate them sharply into primary and secondary processes.

With regard to the primary reaction, although its characters change from day to day and therefore the duration of the action of the irritant must be considered in judging of the appearances met with, yet it will be found that the type of the reaction will depend on the intensity and quantity of the noxious agent. We have referred already to the statement of Schmaus [38], that a slight amount of parenchymatous degeneration is followed by a simple reaction of the neuroglia cells; that in the early stages of a softening caused by an embolus there is a swelling of the tissues and a small emigration of leucocytes; and that with an acute inflammatory softening the tissues become infiltrated with leucocytes and there is an early reaction of the mesodermal tissues. The work of Nissl [24] also demonstrates the variation of the type of cells in reactions following different degrees of irritation. The injection of Indian ink into the subdural space led to the appearance of plasma-cells in the adventitial sheath of the vessels; after producing a localized necrosis of the brain by freezing he found an immense overgrowth of the cells of the intima and of the adventitial sheath of the vessels with the formation of fibroblasts; few plasma-cells were seen in the area of intense reaction, though they were numerous in the sheaths of the vessels in the surrounding tissues. Again, painting the meninges with chromic acid produced necrosis of the subjacent structures associated with the appearance of polymorphonuclear leucocytes in the focus of injury; this was encircled by a collection of fibroblasts, and very few plasma-cells were present except in the zone of tissue limiting the necrosed area. Here we see not only that slight irritations led to the development of plasma-cells, but also that with intense irritation, although the centre of reaction was occupied by leucocytes and fibroblasts, yet outside these where the irritation was less the plasma-cell was again the type of cell present.

Other observers have obtained similar results. Marschalkó [20] introduced small portions of sponge infected with cultures of gonococcus and weak tubercle bacilli into the peritoneal cavity and found later that there were no plasma-cells in the substance of the sponge, but many in the enclosing tissues. Reiz saw them in the brains of rabbits after introducing bits of elder pulp—in fact, the conditions produced by this method resembled those occurring in experimental tuberculosis of the brain. Joannovics [16] expressed his agreement with Marschalkó [20] that these cells are absent in the acute stages of inflammatory processes, but are present in subacute and chronic conditions of all organs: they appear in the recovery stage of acute inflammations. They are of especial interest in gonorrhœa, which has a tendency to subacute and chronic forms; in gonorrhœal affections they are found in the submucous tissues more than near the surface. They are a prominent feature in all infective granulomata; in trichinosis; in the limiting wall of carcinomata. They are not found in the normal brain, but are present in many diseases of that organ, including lues cerebri, phosphorus poisoning, acute alcohol poisoning, status epilepticus and hydrophobia; they can, therefore, no longer be considered pathognomonic of general paralysis.

Now if we turn to the results of our experiments we find valuable support for the view that the character of the cellular reaction found in the nerves and in the spinal cord when the disease-producing agent approaches by the lymph-stream depends entirely on the potency of the irritant, and further, that many of the so-called varieties of cells have one and the same origin. When the capsule had not burst and the tissues were attacked by the toxin only, we found that the reaction produced was of the plasma-cell type, including under that term the numerous intermediate forms which have been described earlier in this paper. But in the other series in which the capsule had burst and the organisms had grown amongst the tissues, there was an altogether different picture. All the cells of the connective tissues and of the walls of the vessels exhibited an intense proliferation with the production of another predominating type of cell, the polyblast; there were also collections of Körnchenzellen showing various stages of development. It will be remembered that in the subacute series there were some polyblasts in the reaction outside the dura mater, i.e., quite close to the capsule. It was at this point that the results of the two series of experiments might be said to have met.

But seeing that in these two series of experiments a culture of the same organism was employed, and seeing also that the experiments were performed on members of the same species of animals, living under identical conditions, and that the animals lived about the same length of time after the operation, we consider that the difference in the reaction in the two series must be attributed to the difference in the intensity and quantity of the irritant. The reactions were produced in both instances by infected lymph which spread by the same path and therefore attacked the same cells. There can be no doubt that if the capsules in the second series of experiments had not burst the reaction would have been of the plasma-cell type, i.e., the type of cells characteristic of the subacute inflammations; but as the capsules had burst and the organisms had grown amongst the tissues, the reaction was of the polyblast type, i.e., the type of the acute inflammations. Now these cells were the direct product of the action of the disease-producing agent and therefore the conditions corresponded to the primary inflammations of Schmaus. But we have shown already that there were small collections of Körnchenzellen, and it is certain that if the animals had lived a little longer and the nerve elements had broken down under the influence of the more prolonged action of the irritant, the tissues would have been infiltrated by these cells and the conditions would have corresponded to the secondary inflammations of Schmaus.

The distinction of the secondary from the primary reaction in the inflammatory process and the recognition that in the secondary reactions the Körnchenzellen have appeared, not as a direct result of the action of the irritant but because of the presence of the degenerated tissues, is a very important step in the elucidation of this question. Not only can a definite stage be recognized by the presence of these cells, but what is even more worthy of notice is that we have in the statements of Friedmann [11] and Schmaus [38] evidence that this type of cell is always associated with a particular function, and that the morphological form they assume is due to the fact that they have imbibed a certain amount of degenerated material. But not all the cells which take up the degenerated material possess the form of a typical Körnchenzell. Friedmann [11], when speaking of the difficulty of distinguishing epithelioid cells from Körnchenzellen, mentioned that the cytoplasm of the epithelioid cell may contain a relatively small amount of fat or of myelin; usually, however, the cell-body is clear and exhibits a network in its protoplasm, or it may be homogeneous. Various forms and sizes of the nucleus and of the cell-body are met with; there may be cells smaller than the typical Körnchenzell, in whose cytoplasm a little fat or myelin may be found, and there may be larger cells in which division often occurs. In these the nucleus is large, amœboid or irregular; or there may be several nuclei in one cell, and in that case the amount of protoplasm is relatively small and is distributed irregularly. We are therefore forced to recognize many forms which are not quite typical of the epithelioid cell or the Körnchenzell.

But it is not only in the removal of disintegrated tissue that the phagocytic action of the epithelioid cell is displayed. Homén [15] has shown that when micro-organisms have to be dealt with, polyblast and epithelioid cells predominate in the tissues. He demonstrated by experiment that injected tubercle bacilli are seen only occasionally in fibroblasts — and under that term he included adventitial cells — or in endothelial cells, and practically never in the neuroglia cells or their derivatives; on the other hand the polyblasts and epithelioid cells or epithelioid polyblasts were active phagocytes, and often contained several bacilli. Now this action in common exhibited by the two forms of cells demonstrates a close relationship between them. This has been recognized by Homén [15] and Wickmann [43], who consider that the epithelioid cells are derived from polyblasts. Fieandt [9] also has stated that epithelioid cells are polyblasts or are derived from them. In our acute series of experiments it was impossible to say where the polyblasts ended and the epithelioid cells began, and it must be remembered that in the acute conditions found in this series the nerve structures had been considerably affected by the irritant, so that products of degeneration were present as well as toxins. But polyblasts are cells which are characteristic of the primary stage of acute inflammatory processes, and they have been shown to be phagocytes of micro-organisms, while epithelioid cells are phagocytes of micro-organisms, and also of disintegrated products of nerve tissues. Further, the origin of the three forms of cells, polyblasts, epithelioid cells and Körnchenzellen has been traced from the cells of the connective tissues, and of the endothelial and adventitial layers of the walls of the vessels. They are therefore so intimately related that their division into three distinct types of cells is purely artificial and arbitrary; they should rather be regarded as three morphological forms of the same cell appearing under different conditions. Now in this connexion it will be remembered that in the subacute series the plasma-cell was the predominating cell, and it also was the offspring of the above-mentioned tissues. The irritant in this series was just strong enough to call forth cells possessing the characteristics of plasma-cells in some areas, while in regions far from the source of the toxin the reaction consisted in a swelling of the nuclei in the adventitial sheath of the vessels, and in a slight increase of the amount of the protoplasm around them; this was evidently the earliest stage of reaction. Outside the dura mater, near the seat of the capsule where the process in this series was most intense, we found some polyblasts and epithelioid cells, many of them containing several nuclei. These were scattered amongst a large collection of plasma-cells, most of which still retained the characters of these cells, while others exhibited various degrees of change which might be considered as intermediate forms between plasma-cells and epithelioid cells. This result, which we have spoken of already as the meeting point of the two series of experiments, will explain the statement of Nissl [24] that the epithelioid cells were derived from plasma-cells.

The precise origin of the cells composing an inflammatory reaction is always a matter of great difficulty, and some points must remain obscure, but a consideration of the mechanism by which the inflammation is produced should prove of very great assistance especially in the case of lymphogenous infections. In experimental lymphogenous infection of the spinal cord of a subacute nature, in which all the inflammatory phenomena are extravascular and the path of the toxic lymph can be traced accurately, we find that besides the proliferation of the connective tissue in the meninges the only structures which react are the adventitial cells of the veins and capillaries and the neuroglia cells immediately in contact with them. The adventitia takes an extremely important part in the production of the cells of reaction; this is not surprising, seeing that the cerebrospinal lymph flows directly into its spaces. Hence when a toxin gains the central nervous system by the lymph path the cells of the adventitial sheath are the part of the vessel to be first attacked; and should the irritant be weak or permeate the tissues slowly no other phenomena need occur for some time. In more acute conditions, however, not only is there a more intense reaction in the tissues already mentioned, but the endothelial cells join in the process; and with a still greater degree of potency of the infection, intravascular changes, such as hæmorrhage and thrombosis, complicate the picture.

But besides the difference in intensity of the reaction in its primary stage the forms of the cells of reaction also vary. Thus it is that in our experiments we find changes ranging from simple swelling of the nuclei, together with a slight increase of the protoplasm around them, to fully formed plasma-cells and polyblasts; and as the process advances these cells often become epithelioid or reticulate in type, and by the imbibition of the products of degeneration, assume the characters of the compound granular corpuscles, which are such a constant feature of the secondary phases of inflammation. The entire reaction, therefore, although it presents several stages, must be recognized as one continuous process.

REFERENCES.

[1] Adami. "Inflammation," London, 1907.

[2] D'Abundo. *Annali di Nevrologia*, Fasc. 3, 4, 1896.

[3] Alzheimer. "Histologische und histopath. Arb. über die Grosshirnrinde," 1909-10, Bd. iii, S. 401.

[4] *Idem. Archiv f. Psych.*, 1898, p. 18.

[5] Beattie. *Journ. of Path.*, 1903, vol. viii, p. 129.

[6] Bonfiglio. "Histologische und histopath. Arb. über die Grosshirnrinde," 1909-10, Bd. iii, S. 359. (Alzheimer, Cerletti, Friedmann, Merzbacher, Nissl, Perusini, Schmaus, Schröder, Sträussler, quoted by Bonfiglio.)

[7] Campbell. *Brain*, 1905, vol. xxviii, p. 367.

[8] Catòla. *Riv. di Patol. nerv. e ment.*, January, 1910, vol. xv, p. 1.

[9] Fieandt. Quoted by Homen.

[10] Forssner and Sjövall. "Über die Poliomyelitis Acuta, samt einem Beitrag zur Neuronophagiefrage," *Zeitsch. f. klin. Med.*, 1907, Bd. lxiii, S. 1.

[11] Friedmann. *See* Flatau, Jacobsohn and Minor, "Path. Anat. des Nervensystems," 1904, Bd. l, S. 468.

[12] Guillain. *See* Cornil et Ranvier, T. 3, p. 719.

[13] Homén and Laitinen. *See* Homén, *Arb. a. d. Path. Inst. zu Helsingfors*, 1902.

[14] Heine. "Beobachtungen über Lähmungszustände der unteren Extremitäten," Stuttgart, 1840.

[15] Homén. *Arb. a. d. Pathol. Inst. der Univ. Helsingfors*, 1910, Bd. iii, H. 1.

[16] Joannovics. *Centralbl. f. Allgem. Path. u. Path. Anat.*, 1909, Bd. xx, S. 1011.

[17] Lewandowsky. "Die Functionen des zentralen Nervensystems," Jena, 1907.

[18] Marie and Morax. *See* Cornil et Ranvier, "Man. d'Histol. Pathol.," 1907, T. 3, p. 721.

[19] Marie and Guillain. *Rev. Neurol.*, 1903, No. 2.

[20] Marschalkó. "Über die sogenannten Plasmazellen," &c., *Arch. f. Dermat. u. Syphil.*, 1895, Bd. xxx, S. 241.

[21] Martin. "La maladie du sommeil et les troubles mentaux," &c., *Ann. de l'Inst. Pasteur*, 1911, T. xxv, p. 463.

[22] Mott. "Psychiatrical Congress, Berlin, October, 1910," *Proc. Roy. Soc. Med.*, November, 1910.

[23] Mönckeberg. "Anat. Befund eines Falles von Landryschen Symptomcomplex," *Münch. med. Wochenschr.*, 1903, Bd. l, S. 1958.

[24] Nissl. "Histologische und Histopath. Arb. über die Grosshirnrinde," 1904, Bd. i, H. 1.

[25] Orr. "A Contribution to our Knowledge of the Course of the Lymph-stream in the Spinal Roots and Cord," *Rev. of Neurol. and Psychiat.*, 1903, vol. i, p. 639.

[26] Orr and Rows. "Systemic Lesions of the Posterior Column of the Spinal Cord, &c.," *Brain*, 1904, vol. xxvii, p. 460.

[27] *Idem.* "Lesions of the Spinal Cord the Result of Absorption from localized Septic Foci, &c.," *Rev. of Neurol. and Psychiat.*, 1906, vol. iv, p. 25.

[28] *Idem.* "A Clinical and Experimental Investigation into the Lymphogenous Origin of Toxic Infection of the Central Nervous System," *ibid.*, 1907, vol. v, p. 345.

[29] *Idem.* "The Histological Evidence that Toxins reach the Spinal Cord via the Spinal Roots, with Special Reference to Plasma-cells," *ibid.*, 1910, vol. viii, p. 721.

[30] *Idem.* "Subacute and Acute Inflammatory Reactions produced in the Spinal Cord by Infection of its Lymph-stream," *ibid.*, 1912, vol. x, p. 405.

[31] *Idem.* "Further Observations on the Influence of Toxins on the Central Nervous system," *Proc. Roy. Soc. Med.*, 1913-14, vol. vii, Sect. Psychiat., p. 21.

[32] Orr, Rows, and Stephenson. "The Spread of Infection by the Ascending Lymph-stream of Nerves from Peripheral Imflammatory Foci to the Central Nervous System," *Rev. of Neurol. and Psychiat.*, 1913, vol. xi, p. 349.

[33] Pappadia. *Riv. di Patol. nerv. e ment.*, 1909, vol. xiv, p. 337.

[34] Pirrone. *Ref. Med.*, 1905.

[35] Redlich. "Beitrag zur pathol. Anat. d. Poliom. ant. acuta infantum," *Wien. klin. Wochenschr.*, 1894, Bd. vii, S. 287.

[36] Righetti. *Riv. di patol. nerv. e ment.*, 1909, vol. xiv, p. 385.

[37] Römer. "Die Epidem. Kinderlähmung," Berlin, 1911.

[38] Schmaus. "Die Anwendung des Entzündungsbegriffes auf die Myelitis," *Deutsche Zeitschr. f. Nervenheilk.*, 1904, Bd. xxvi, S. 390.

[39] Sicard and Bauer. Cornil et Ranvier, T. 3, p. 719.

[40] Spitzer. *Arb. a. d. neurol. Inst. a. d. Wien. Univ.*, 1912, Bd. 19, H. 3,

[41] Unna. "Über Plasmazellen insbesondere bei Lupus," *Monatschr. f. prakt. Derm.*, 1891, Bd. xii, S. 296.

[42] Wickmann. *Arbeiten a. d. Patol. Inst. der Univ. Helsingfors*, 1905, Bd. i, S. 109.

[43] *Idem.* "Weitere Studien über Poliomyelitis acuta," &c., *Deutsche Zeitschr. f. Nervenheilk.*, 1910, Bd. xxxviii, S. 396.

[44] Zalla. "La nevrite ascendente," Firenze, 1913.

[45] Ziveri. *Riv. de Patol. nerv. e. ment.*, 1913, Fasc. 5.

UNUSUAL TYPE OF HEREDITARY DISEASE OF THE NERVOUS SYSTEM (PELIZÆUS - MERZBACHER), APLASIA AXIALIS EXTRA-CORTICALIS CONGENITA.

BY FREDERICK E. BATTEN, M.D., AND DOUGLAS WILKINSON, M.D.

INTRODUCTION.

THE disease about to be described is a familial and hereditary one, having its onset in the first three months of life, even if it is not actually congenital. It presents symptoms which in many respects are similar to those seen in cases of disseminated sclerosis, cerebellar disease, and in its later stages to Friedreich's disease. It is very slowly, if at all, progressive, affects chiefly males, and is transmitted by healthy females. In the family here described males only are affected. It corresponds to none of the commonly recognized types of familial affection, but the symptomatology so closely resembles that presented by the family recorded by Pelizæus and Merzbacher, that we believe the disease to be of the same nature, although no pathological examination has been made in any member of the family here described. The cases published by Nolan also resemble these cases clinically, but no pathological examination has been made.

When the children were first seen we were inclined to associate the condition with some congenital defect in the development of the cerebellum, such as occurs in litters of cats and puppies, and have been recorded by Herringham, Andrewes, Risien Russell, and others, but after studying the pathological anatomy as put forward in Merzbacher's excellent paper, we have come to the conclusion that our cases probably belong to that group.

CLINICAL AND FAMILIAL FEATURES.

The family history is best studied from the following tree, the usual signs being used. The numbers below the affected individuals refer to the number of the case in the text.

The family first came under notice when two boys, aged 4 and 2, were admitted into the Hospital for Sick Children, Great Ormond

Street, in November, 1913. The family history as obtained from their mother was as follows :—

W. J. W., father of Cases 3 and 4 and grandfather of Cases 1 and 2, appears to have been normal. He married, had twelve children, and died of phthisis in 1905. As he was born in Yorkshire his wife does not know any of his family, but to the best of her knowledge they are all dead. Her family are all quite normal, and since the death of her first husband (W. J. W.) she has married again and has given birth to a normal son.

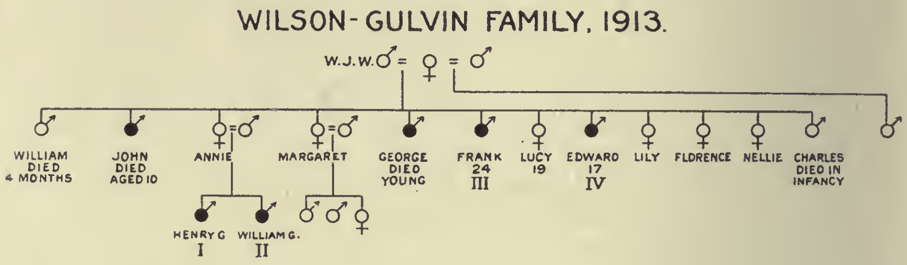

Fig. 1.

Details of the Twelve Children.

(1) William, died at the age of 4 months of convulsions.

(2) John, lived to the age of 10; he could not sit up or talk properly, was subject to fits, and died of a brain abscess (?).

(3) Annie, is the mother of Cases 1 and 2; she is quite normal, and appears to be of more than usual intelligence.

(4) Margaret, is well and married; she has two boys and a girl who are quite normal.

(5) George, died as a baby; he is thought to have been like the patients.

(6) Frank (Case 3).

(7) Lucy, is well, aged 19; she is not married.

(8) Edward (Case 4).

(9) Lily, died as an infant of pneumonia.

(10) Florence, is well and unmarried.

(11) Nellie, is well and unmarried.

(12) Charles, died as an infant; nothing is known of his condition.

In addition to the above children there were three or four miscarriages.

CASES.

Case 1.—Henry G., aged 3 years 9 months. Was a full-time child, breast-fed for nine months. He never had any acute illness or fits. He is rather small for his age. He is generally a quiet child, but when he does cry he is extremely noisy and persistent. He does not appear to take much interest in anything, and cannot talk. The mother says that while he cannot say any words clearly except "Mum" and "Dad," yet he makes sounds which she can understand. He will take hold of a piece of paper with either hand, and in so doing shows a slow ataxic tremor of the whole arm.

Eyes.—There is a constant concomitant wheel nystagmus, which is not increased by looking in any direction. In this movement the pupils describe an ellipse with the long axis horizontal. There is no rotation of the eyes on their horizontal axes. The pupils are equal, regular in outline, central, react to light, and appear to react to accommodation. Vision seems good, and the fundi appear normal.

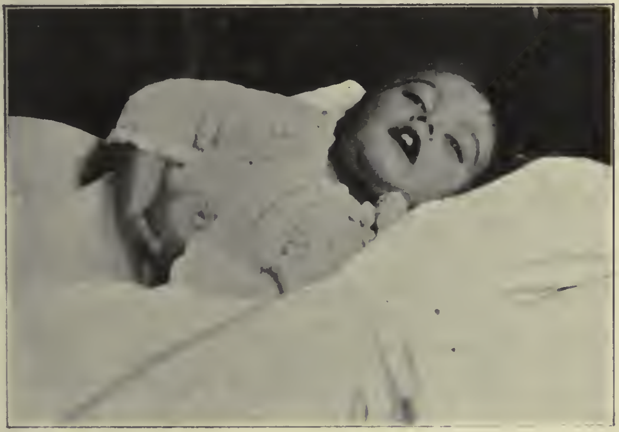

FIG. 2 shows the appearance of one member of the second family.

The boy restrains the movements of the hands by clasping them together and pressing them against the trunk. Note the normal appearance of the shape of the forehead.

Motor.—While the child can move all his limbs and also the head from side to side, he cannot sit up, nor can he support the head when sat up. When placed in the sitting position there is a slow nodding tremor of the head which falls forward on to the chest, and in this position the nystagmus becomes slightly more marked. There is some ataxia of the legs, but owing to their greater weakness it is not so marked as that in the arms. There is a slight degree of hypotonia in both legs and arms.

Reflexes.—The knee- and ankle-jerks are present. The plantar response is of an extensor type. The superficial abdominal reflexes cannot be obtained. There is no abnormality in the contour of the head or vertebral column. The mouth is rather crowded with poorly developed teeth, and the palate is rather arched. Swallowing is quite normal, but the boy cannot feed himself. The chest is poorly formed, there being well marked lateral grooves and depression of the lower end of the sternum. There is generalized bronchitis present, with a loose and frequent cough, but no expectoration. On the skin of the chest and arms there are several patches of lupus, and there is a dactylitis of the first phalanx of the little finger of the left hand, which is possibly tuberculous. At night the child frequently has profuse sweats. The boy gives no indication of his desire to pass urine or fæces.

Case 2.—William G., aged 2 years 1 month, was born at full time, and was breast-fed for a year. Neither in this case nor in that of his elder brother was labour difficult or tedious. He has always been "delicate," but has never had any illness, convulsion, or fit. While he is a well grown child his legs appear to be less well developed than his arms. He is a restless and irritable child, often moving the head from side to side and crying loudly and persistently. He appears to take very little interest in his surroundings, but a piece of paper attracts him, and he will grasp it with the left hand, but then only moves it about in a purposeless manner, showing a slow ataxic tremor of the arms as he moves.

Eyes.—The eyes are in every respect exactly similar to those of Case 1.

Motor.—The child can move all his limbs, but the legs are weak. He prefers the left hand to the right, and appears unable to grasp with the latter. He cannot sit up unsupported, nor can he support the head when sat up. On voluntary movement he shows the same slow tremor that is present in Case 1. There is slight general hypotonia. In addition to the tremor the child shows curious, almost athetoid, movements of the fingers before grasping an object.

Reflexes.—The knee-jerks are present, but no ankle-jerks can be obtained. The plantar responses are of the infantile extensor type. The superficial abdominal reflexes cannot be elicited.

There is no abnormality in the contour of the skull or vertebral column. The teeth are only partially erupted (there are eight in the upper and four in the lower jaw) and are poorly formed. The palate is very arched. Swallowing is performed quite normally. The child has to be fed.

The similarity of these two cases is very striking; their expression, attitude, reflexes, &c., are in almost every particular identical, and with the exception of the lupus and a slight difference in size it would have been difficult to distinguish between them. Both showed a slight relative under-development of the lower part of the body, the legs being disproportionately small.

Case 3.—Frank W., aged 24, inmate of B—— Asylum, uncle of the above, has been affected with the disease from which he suffers from birth, and his condition is now the same as it was when he entered the asylum some years ago.

He is friendly, and appeared rather pleased to be examined, smiling most of the time. While he understands what is said to him well enough to carry out simple orders—he picked up a penny from the counterpane, transferred it to the other hand, and finally handed it to the owner—he is obviously impaired mentally. He cannot feed himself owing to his tremor.

Speech.—He is said never to talk spontaneously, but attempts to answer questions quite willingly. His articulation is so imperfect that little of what he says can be understood by those unaccustomed to his speech.

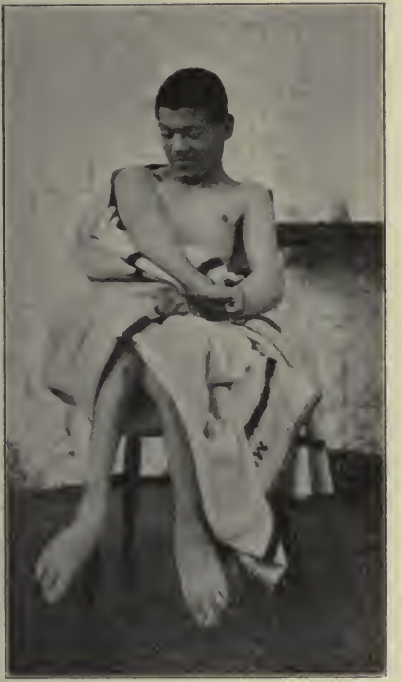

FIG. 3.

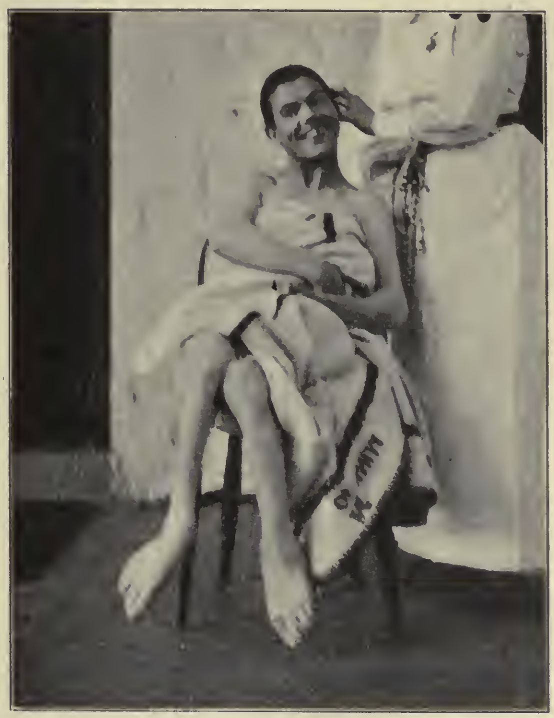

FIG. 4.

Figs. 3 and 4 show the appearance of F. W., aged 24. They show the well-developed arms, the wasted legs and the position of the feet.

The constant movement and overaction is in part shown in fig. 3, by the position of the right arm, and in fig. 4 by the facial expression.

Eyes.—The pupils are regular, react to light and accommodation. There is no strabismus, nor any apparent ocular muscle weakness. There is a constant concomitant, wheel nystagmus, which is unaltered by any movement of the eyes. There is no rotation of the eyeballs in this nystagmus. Vision appears to be good and the fundus normal.

Hearing is good.

The tongue is protruded rather jerkily, but appears normal otherwise. Sensation does not appear in any way impaired.

Motor.—While the arms and chest are well developed, and even surprisingly muscular, the legs are wasted and thin, especially below the knees. The patient uses the arms to turn over in bed, &c. He cannot stand or sit up in bed unassisted. The legs are kept constantly flexed at the knees and hips, and there is a considerable degree of adductor spasm. The feet are flattened with a tendency to eversion of the soles and slight foot drop. Movement of the legs is very feeble. On performing any movement a slow, wavy tremor is at once apparent; this is best seen on sitting up, when, in the effort to support himself, rotary and nodding movements of the head become very marked. There is also a well-marked slow tremor of the arms on attempting any movement. A tendency to hypotonia is shown by the fact that the feet can easily be flexed to less than a right angle, but on the other hand the arms are held rather stiffly and there is a slight delay in relaxing the grip.

Reflexes.—The knee-jerks are present, the right more marked than the left. There is bilateral ankle-clonus. The deep reflexes are easily elicited in the arms. The superficial abdominal reflexes are absent. The plantar response is definitely extensor on the right, indefinite on the left. Sphincter control is good, but at night there is occasionally incontinence, probably because he fails to attract the attention of an attendant.

The skull is well formed, except that the occiput is rather flat; the circumference is 20 in., and from meatus over the vertex is nearly 15 in. There is a mid-dorsal scoliosis, the convexity to the right.

Case 4.—Edward W., aged 17, brother of the last case; inmate of S—— Workhouse Infirmary. He has been affected since birth, and so far as can be ascertained his condition has not altered.

He resembles his brother in appearance and disposition, but seems to be rather more intelligent. He is said to take considerable interest in the other members of the ward, and to talk to them. When he heard us mention his brother he said that Frank was like himself. He also carried out simple orders, picking up coins, &c. But he showed a very imperfect idea of their relative values, in that when offered a penny or a sixpence he preferred the penny.

Speech is very imperfect, but he attempts longer sentences, and is more easily understood than his brother. In speaking there is well-marked overaction of the facial muscles. One of his sentences was:—

"When you co͞omed in I we͞er go sle͞ep."

Eyes.—The pupils are equal, and react normally to light and accommodation. There is no strabismus, but a wheel nystagmus identical with that shown by the other three cases. Vision appears good, and the fundi are normal.

Hearing is normal. The tongue appears normal, but there are jerky movements in protruding it. Sensation is not impaired. While he is fatter than Case 3, his muscular development in the arms is not nearly so good. He cannot sit up unassisted, or stand at all. The legs are kept flexed at the knees and hips, but the flexion is less marked than in Frank. There is also some adductor spasm, but again less than in the brother. There is foot-drop, the feet being of the cavus shape, with some inversion of the anterior part of each. The legs are wasted, and in proportion to the arms very thin (this disproportionate thinness of the legs is more marked in Frank). The tremor which is evoked by any effort is the exact counterpart of that seen in Frank, but slightly more marked. Head nodding and rotation are also present. There is no hypotonia in this case.

Reflexes.—The superficial abdominal reflexes are absent, and the plantar response is definitely extensor on both sides. The knee-jerks are both exaggerated; the testing of the left elicits a knee-clonus. The ankle-jerks are present, and ankle-clonus can be obtained. He is occasionally incontinent at night, but otherwise has good sphincter control.

There is some flattening of the occiput, but otherwise the shape of the skull is normal. Circumference 20¼ in.; measurement from meatus to meatus, over the vertex 14 in, There is no spinal curvature in this case.

One of the most striking features in these cases is the similarity of their conditions. Edward and Frank resemble one another very closely indeed, as do Henry and William. All four patients show identical tremor and nystagmus, the latter of an unusual type; all have disproportionately small lower extremities, and none of them had superficial abdominal reflexes. Three of them showed some hypotonia, and all had extensor plantar responses. With regard to the mental condition in Cases 3 and 4, the defect seemed to us more apparent than real, and we were impressed with the idea that both are capable of considerable improvement if only they could be patiently and systematically taught.

The cases described by Pelizæus in 1885 closely resemble those of the family which we describe. In his family there were five cases in the children and grandchildren of one pair; three were dead and two were living at the time of the publication. All those affected were males, the disease being transmitted by unaffected females. The symptoms resemble those seen in disseminated sclerosis, tremor of the head, nystagmus, ataxia, slow speech, and spastic paralysis of the lower extremities.

There was also mental impairment, but it was more apparent than real. Sensation and control of the sphincters were normal.

The disease was present in earliest infancy, and was not progressive, the patients dying of some intercurrent disease between the ages of 20 and 30.

Merzbacher, in 1908, followed up this family, and found twelve instances of the disease, one of which he was able to investigate pathologically and report in a further paper entitled "Eine eigenartige familiär-hereditäre Erkrankungsform (Aplasia axialis extracorticalis congenita)," published in 1910. He gives a family tree and further details with regard to this family which is republished here.

There are several discrepancies when compared with the tree originally published by Pelizæus, but the points that are brought out are: (1) that this disease has been observed in four generations; (2) that fourteen members of the family are known to be affected; (3) that it is always transmitted by healthy females; and (4) that males are more likely to be affected than females; only two of the fourteen individuals affected were females.

CONGENITAL FAMILIAL DISEASE, PELIZAEUS-MERZBACHER, APLASIA AXIALIS EXTRACORTICALIS CONGENITA

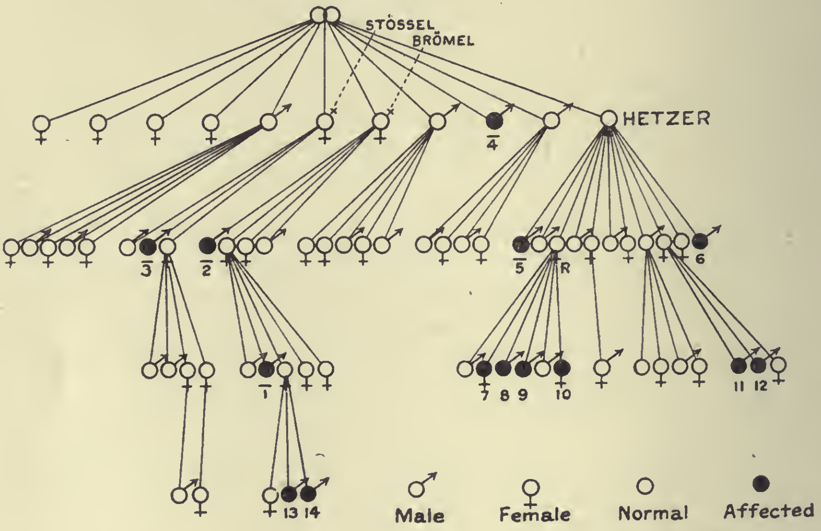

FIG. 5.

The clinical characters of the affection are given as follows:—

The disease begins in the first months of life; it makes rapid progress till the sixth year, then is more slowly progressive. When the disease is fully developed, it shows itself by nystagmus, slow speech, difficulty in the carrying out of motor impulses, disturbance of succession and co-ordination of movements, ataxia, intention tremor, "Mitbewegungen," masque-like facial expression, paresis of the back, pelvic and abdominal muscles, paralysis and spastic contraction of the lower extremities, increase of the patella reflexes, Babinski response, loss of abdominal reflexes.

The following symptoms often accompany the above: trophic disturbance of the bones, vasomotor disturbance in the lower extremities, loss of mental capacity. The affected individuals may reach old age, and only die of some intercurrent disease.

The pathological condition was as follows:—

A normally convoluted brain, but small in all dimensions. The cerebellum, pons, and medulla appeared to be most affected in their size.

In the midline of the cerebrum the atrophy of the corpus callosum and fornix was most striking; so marked was this that on superficial inspection a defect of the corpus callosum was suspected. Sections through the brain showed that the smallness of the hemisphere was due to marked atrophy of the white substance alone. Corpus callosum and fornix were present, but very much atrophied; the anterior commissure was, on the other hand, well developed. The grey substance of the brain was of normal appearance.

In the section without further treatment one could observe isolated longish spots which lay in the white substance. These spots were shown by the Weigert-Pal method to be due to the fragmentation of the sheath of the medullated nerves.

In the central white matter of the various portions of the hemisphere and in some convolutions there were only small portions of normal fibre bundles remaining, and this gave the preparation a speckled appearance. These single remaining portions of the original tracts appear to be so disposed one to another that one island might be regarded as a continuation of its neighbour; thus a continuity of the medullary substance was rendered for the most part possible by the aid of the islands.

The most affected parts were the corona radiata and the corpus callosum, the great association systems were less affected. In the frontal, occipital, and temporal lobes and in the cerebellum the atrophy of the medullated fibres was most marked. Between the islands of the medullated fibres lay an unstained ground-substance. The collection of axis cylinders corresponded to the dissemination, size and extent of these medullated islands, and they too have suffered an apparent interruption in their continuity. The medullated fibres of the cortex and remaining grey substance showed no pathological change. The internal and external capsule, the crus, the pons, &c., were full of normal fibres.

The intact condition of certain bundles in the immediate neighbourhood of the cortex (Fibræ arcuatæ Meynert) was especially striking. The unstained ground-substance was composed of glia tissue. The structure conditions vary in different localities. Active proliferation of the glia was never present (except in the optic thalamus).

The destruction and absorption of other tissues has made the presence of the glia substance striking. It is believed that the unstained tissue contains very fine axis cylinders, and that the interruption of these was only apparent. Neither in the ganglion cells nor in the cortex were any pathological changes visible.

Sections of the medulla showed only a partial destruction of some system; no island formation was present. The cerebellar paths were most involved.

Merzbacher deals with a case recorded by Müller presenting somewhat similar symptoms, but differing pathologically, and concludes with a consideration of the whole question of hereditary degeneration.

In 1895 Nolan recorded three cases in a family whose genealogical tree is appended. In many ways these cases resembled those which we have described. They showed disease from birth, constant nystagmus, ataxia, and speech defect. One had increased knee-jerks, and bilateral ankle-clonus, but the other two showed loss of knee- and ankle-jerks. None of them could walk unaided, and two could not stand unassisted. They had no sphincter affection, no lightning pains, no foot deformity, and no sensory defect; differing from typical cases of Friedreich's disease in the early onset and slight increase of symptoms.

Their mental condition also was similar to that of the patients we describe, for, while they were backward, they showed none of the dirty habits, waywardness, or sexual depravity so often associated with congenital idiocy. They never spoke unless spoken to, but tried to answer questions, were of a cheerful aspect, and seemed pleased when noticed; in fact their defects seemed to lie chiefly in initiation and memory. In the following points, however, they differ from our cases; one patient was a female, and they all showed some indefinite wasting of the hands, flattening of thenar and hypothenar eminences, and some slight suggestion of "main en griffe." They were said to have shown some increase of symptoms, but their condition remained almost if not quite stationary after admission to the asylum.

Since these patients were recorded the two eldest members of the generation which produced them have married. Sarah has three children, of whom one, a daughter, is ataxic and "simple." David has two sons who show speech defects. Unfortunately the details which can be obtained of these children are meagre.

Two of the patients described have since died of phthisis, and the third is at present suffering from the same disease. *Post-mortem* examinations were not permitted.

In conclusion, we are indebted to Dr. Cowan and Dr. Wolseley Lewis for their kindness in facilitating our access to two of the cases, and to Dr. Nolan for further details of his cases. It is hoped that some day we shall be able to confirm our view as to the nature of these cases by a pathological examination.

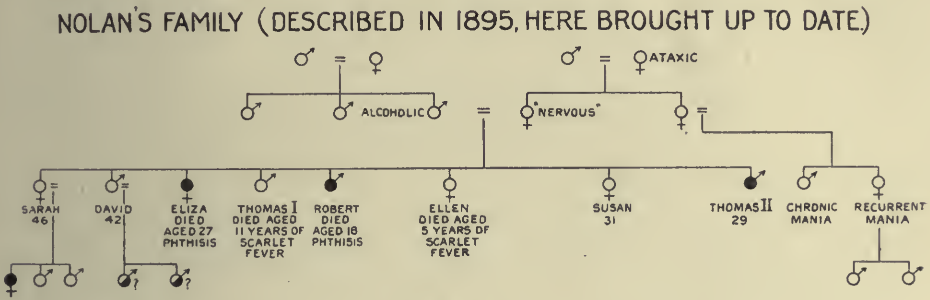
NOLAN'S FAMILY (DESCRIBED IN 1895, HERE BROUGHT UP TO DATE)
♂ = ♀
♂ = ♀ ATAXIC
ALCOHOLIC
=
"NERVOUS"
=
SARAH 46
DAVID 42
ELIZA DIED AGED 27 PHTHISIS
THOMAS I DIED AGED 11 YEARS OF SCARLET FEVER
ROBERT DIED AGED 18 PHTHISIS
ELLEN DIED AGED 5 YEARS OF SCARLET FEVER
SUSAN 31
THOMAS II 29
CHRONIC MANIA
RECURRENT MANIA
?
?

FIG. 6.

SUMMARY.

A familial and hereditary disease, having symptoms resembling disseminated sclerosis, is described. Six males at least were affected in two generations. The subjects of this disease are almost always males, and the condition is transmitted by unaffected females. Those affected are either congenitally diseased or exhibit symptoms in the first months of life, the progress of the disease being very slow. They are mentally defective and ataxic, show nystagmus, speech defect, and defective development, with weakness and spasticity of the lower limbs. It is considered probable that these cases belong to the type of familial disease described by Pelizæus and Merzbacher under the title "aplasia axialis extracorticalis congenita."

BIBLIOGRAPHY.

HERRINGHAM and ANDREWES. *St. Bart.'s Hosp. Reports*, 1888, vol. xxiv, p. 241.
MERZBACHER. *Med. Klinik*, 1908, Bd. iv, H. 2, S. 1952.
Idem. *Zeitschr. f. d. ges. Neurol. u. Psychiat.*, 1910, Bd. iii, S. 1. [This paper was republished as a pamphlet. Berlin: Springer, 1910.]
NOLAN. *Dublin Journ. Med. Sci.*, 1895, p. 1.
PELIZÆUS. *Arch. f. Psychiat.*, 1885, Bd. xvi, S. 678.
RUSSELL, RISIEN. *Brain*, 1895, vol. xviii, p. 52

AN ANATOMICO-PHYSIOLOGICAL STUDY OF THE POSTERIOR LONGITUDINAL BUNDLE IN ITS RELATION TO FORCED MOVEMENTS.

BY L. J. J. MUSKENS, M.D.

Amsterdam.

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INTRODUCTION.

In previous investigations respecting the circus and rolling movements occurring in different species of vertebrates, I had observed the important part played by the posterior longitudinal bundle, when injured, in producing these phenomena [107,113]; I resolved therefore to make special experiments in this subject, and by means of the Probst "concealed needle" I made lesions in all directions, chiefly in cats, in the area between the nucleus of the abducens nerve and the posterior commissure. In each case the forced movements were noted, whether in the horizontal plane (circus movements) or in the plane vertical to the longitudinal axis of the animal (rolling movements). Forced movements were considered to be present, first, so long as the head and eyes remained deviated or so long as there was an inclination to go to one side, circus movements in a slight degree; and secondly, as long as there was an inclination to lie down or to fall to one side, which I look upon as a slight manifestation of rolling movement. The character of the movements and the direction of the locomotion which is the consequence of them are determined in accordance with the normal anatomical position of the animal, the normal posture being always reduced to that of the primary vertebrate exhibiting the simplest forced movements, for instance the fish.

A rolling movement exhibited by a patient, therefore, which commences with the turning of the chin to the left shoulder is, according to my nomenclature, a rolling towards the right, for, after reducing the posture and the movement to that of the primary vertebrate, this movement produces locomotion to the right from the original position of the animal.

The significance of the exact direction of the forced movement becomes at once apparent as soon as we begin to study the different pathological conditions of the ocular movements, conjugate deviation of head and eyes, and other neurological syndromes.

During my experiments, it was found necessary to draw a sharp distinction between forced movements in the horizontal plane, or circus movements, and those in the plane vertical to the longitudinal axis of the animal, or rolling movements. Various combinations of movements, however, were by no means infrequent, so that different animals appear in the table more than once; the character of the forced movements present being employed as a means of dividing them into groups.

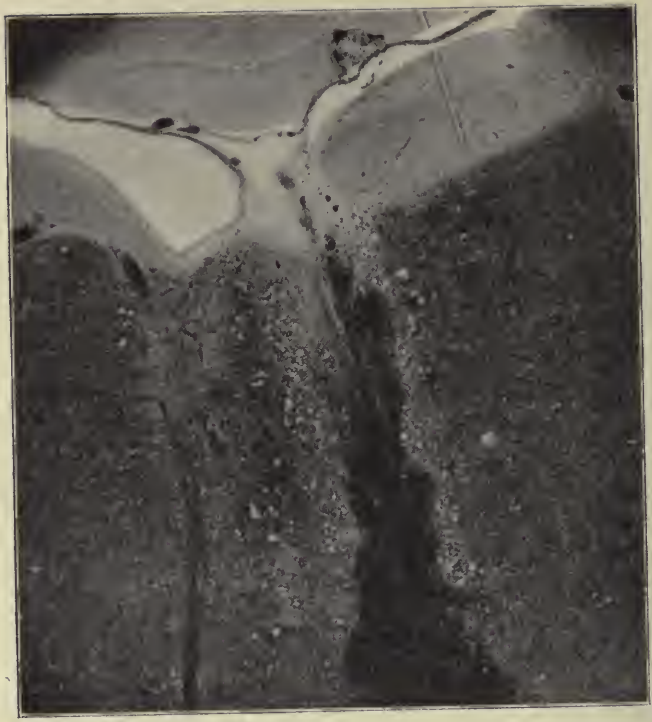

Fig. 1*a*.

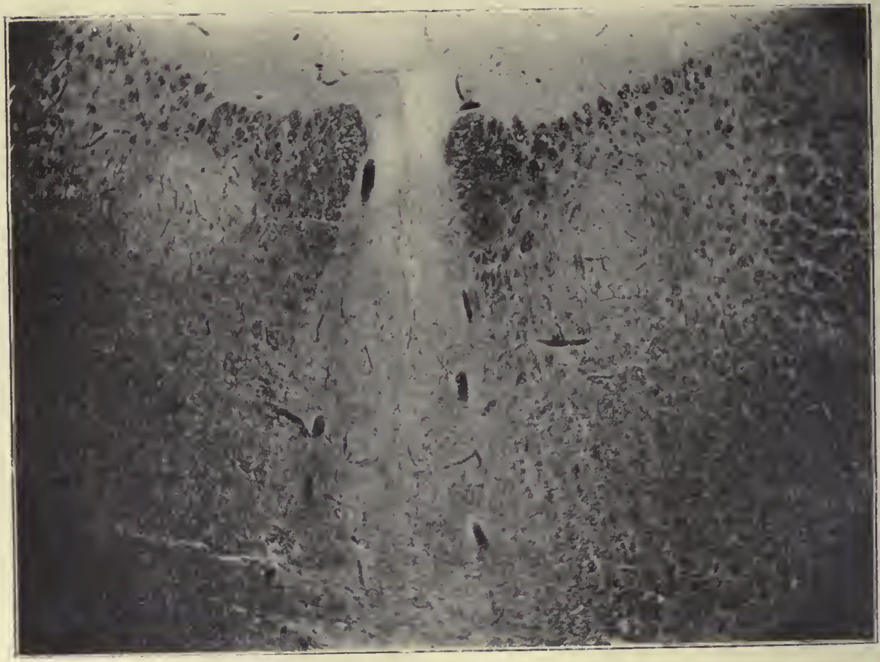

Fig. 1*b*.

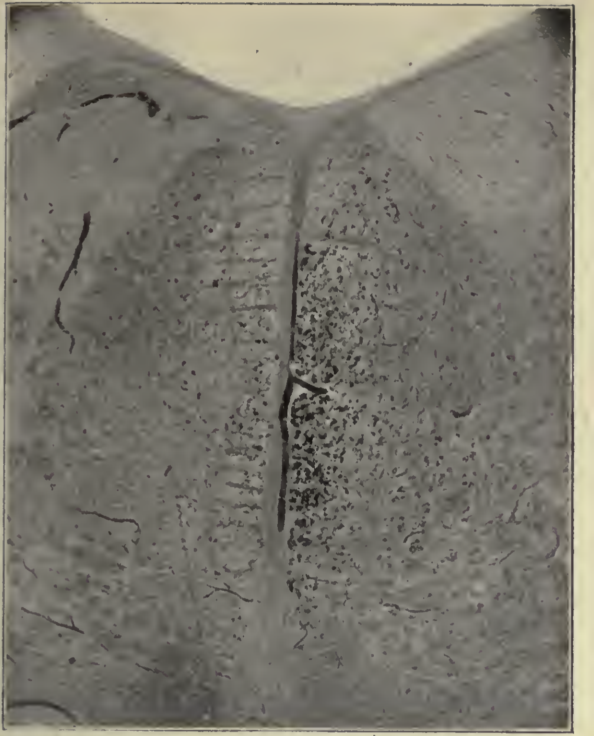

Fig. 1*c*.

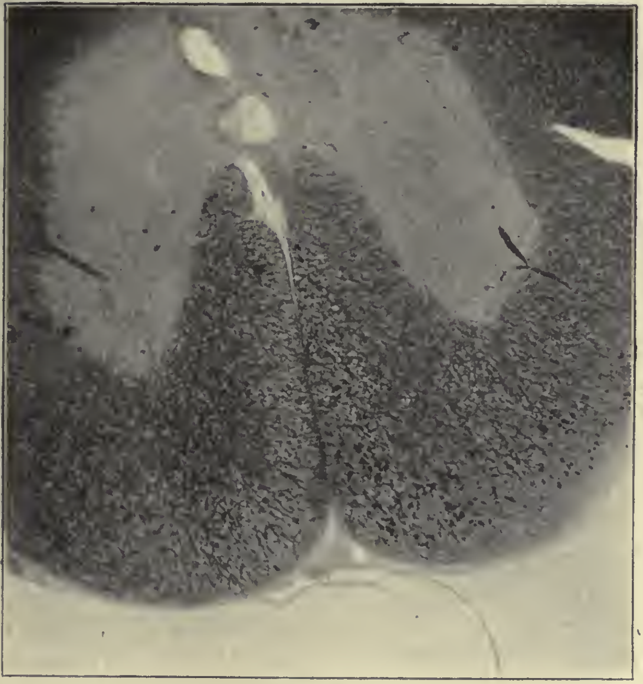

Fig. 1*d*.

FIGS. 1*a*, 1*b*, 1*c*, 1*d*.—Cross sections of cat No. 139.

Fig. 1*a*.—Stab through the posterior longitudinal fasciculus in the pontine region.
Fig. 1*b*.—Ascending degeneration in the region of nuc. tegmenti profundus.
Fig. 1*c*.—Descending degeneration in the medulla oblongata.
Fig. 1*d*.—Descending degeneration in the medulla spinalis dorsalis.

CHAPTER I.—SECONDARY VESTIBULAR CONNEXIONS AND FORCED MOVEMENTS IN THE HORIZONTAL PLANE (CIRCUS MOVEMENTS).

§ 1.—*Lesion of the Mesial Part of the Posterior Longitudinal Bundle on one Side* (*Table I, Group* 1, *p.* 376).

In order to analyse the physiological functions of the different parts of the posterior longitudinal bundle, I endeavoured first to divide its mesial part on one side proximal to the sixth nucleus. In this I was successful in three animals (Nos. 91, 119 and 139); in one of these (No. 91) the lateral horn of the bundle was injured as well. Fig. 1 illustrates the lesion in the pons in one of these experiments and the resulting ascending and descending degenerations (cat No. 139).

In these animals circus movements towards the side opposite the lesion were observed for longer or shorter periods. This agrees with the results obtained by other investigators (*see* Table, Group 1) and is in harmony with the observations of Schiff and Probst that a hemisection of the pons causes circus movements to the intact side, but it would seem to show further that a total hemisection is not necessary in order to produce these movements, a lesion of the mesial part of the posterior longitudinal bundle being sufficient.

In all these cases there was a definite cerebro-petal degeneration in the posterior longitudinal bundle on the side of the lesion. This degeneration involved thick fibres which occupy a fixed position in the bundle, namely, in its mesial part and which correspond very closely in situation to the ascending bundle that, according to Thomas, Russell, Probst, Fraser, Lewandowsky, and van Gehuchten, is found degenerated after a lesion of Deiters' nucleus. Not infrequently some of the fibres of this latter bundle are found outside the actual area of the posterior longitudinal bundle and especially to its ventral side (Table I, No. 139 and No. 158). It ends close to the nucleus of the posterior commissure and appears to give off a number of fibres to the third nucleus. As far as I can judge from my own observations and those of others, these anatomical and physiological relationships are constant, and they suggest that we have to do here with an ascending vestibulo-mesencephalic bundle which controls circus movements to the opposite side.

A definite descending degeneration was present also in these animals. It was more pronounced on the side of the operation and could be followed on that side to the lumbo-sacral region in the antero-lateral column of the cord. On the other side, however, a few fibres were degenerated; these were situated more ventrally and laterally (Probst and van Gehuchten's reticulo-spinal bundle).

In the medulla, both these descending tracts leave their dorsal position in the posterior longitudinal bundle, and, according to Hösel, Probst, Winkler, Economo, and Karplus, take up a more ventral position. According to Wallenberg, the same change of position occurs in pigeons. Fraser observed it also in his experiments, but it must be borne in mind that he injured the posterior longitudinal bundle at the spot where the fibres enter it from Deiters' nucleus.

We shall have to consider presently the anatomical connexions of these descending fibres of the posterior longitudinal bundle. In order to simplify the narration of my results, however, I shall merely specify here what fibres were found degenerated. They were :—

(1) The descending fibres which, according to Held, Boyce, Redlich, van Gehuchten, Probst, Economo, and Karplus, degenerate on the side of the operation after lesion in the vicinity of the posterior commissure.

(2) Homolateral ponto-spinal or reticulo-spinal fibres which degenerate downwards after lesion of the substantia reticularis of the pons, as discovered by Probst, and confirmed by Lewandowsky and van Gehuchten.

(3) Heterolateral fibres constituting the crossed reticulo-spinal bundle which is found degenerated after lesion of the substantia reticularis of the pons (Kohnstamm, van Gehuchten).

§ 2.—*Lesion of the Posterior Longitudinal Bundle on both Sides* (*Table I*, *Group* 2, *p*. 376).

In a number of cats, I endeavoured to divide the mesial parts of both posterior longitudinal bundles and succeeded in doing so in four animals (Nos. 90, 92, 97, 114) ; in one of these (No. 114) they were divided in the neighbourhood of the posterior corpora quadrigemina, together with both lateral parts of the bundle (fig. 2) ; in another animal (No. 92) the mesial part of the posterior longitudinal bundle was cut on both sides, on the left somewhat frontally as compared with the right, and at the same time the lateral part also was divided on the left side (fig. 12). Three of these animals were incapable of locomotion ; they could neither stand nor run, and their condition in many ways resembled that of rabbits during the first period after extirpation of both labyrinths (Winkler). There was conspicuous absence of lateral conjugate eye movements.[1]

---

[1] Observations on pathological cases with comparable symptoms and probably a similar lesion of the posterior longitudinal bundle have been recorded also by Parinaud, Priestley-Smith, Sauvineau Nieden, Long, Schöler, and Spiller.

In animal No. 90 both posterior longitudinal bundles were cut right across at the level of the exit of the trigeminal nerve except for the lateral part of the left bundle (figs. 11*a* and 11*b*, p. 387). In this case hæmorrhage took place exactly at the section of the left bundle, and this probably irritated the fibres without completely destroying them. At any rate, both the ascending and the descending degeneration was less pronounced on the left side, where the hæmorrhage occurred, than on the right side, where the bundle was cut across without hæmorrhage. This was the only animal in this group that was able to perform circus movements (to the right) ; it had also conjugate deviation of the head and eyes to the right for six days.

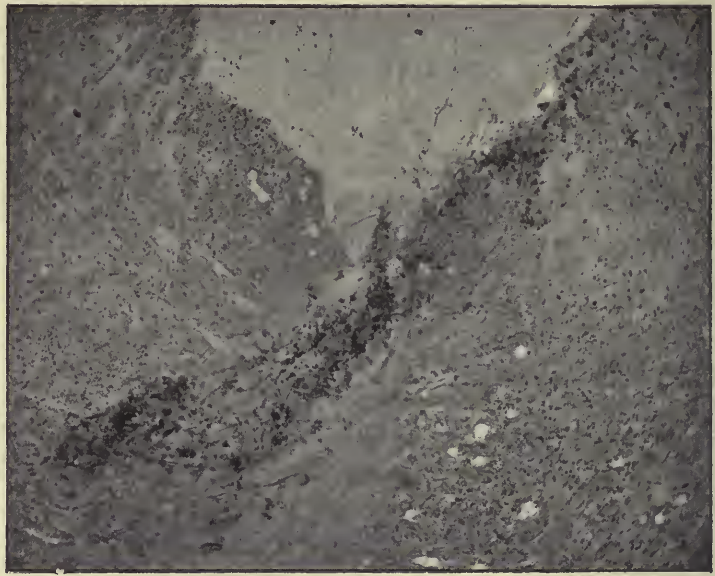

Fig. 2.—Lesion in the region of the corpora quadrigemina posteriores of cat 114.

After the operation, in all these cases of lesion of the middle parts of both posterior longitudinal bundles, there was present on both sides an ascending and descending degeneration in the areas described in the first group, where the lesion was unilateral. A lesion of both longitudinal bundles in the region of the posterior corpora quadrigemina produces forced movements in a vertical plane coinciding with the longitudinal axis of the animal, such as staggering and tumbling, which are not discussed in this paper.

§ 3.—*Lesion of Different Parts of Deiters' Nucleus* (*Ventral or Triangular Part, and Dorsal or Larger-celled Part*) (*Table I, Group* 3, *p.* 376).

We must consider whether the supposition that we have to deal with a vestibulo-mesencephalic tract in the mesial part of the posterior longitudinal bundle is correct; in other words, whether this mesial part is actually identical with the crossed vestibulo-mesencephalic bundle of Fraser, Hösel and van Gehuchten.

For this purpose we have at our disposal two experiments with lesions of different parts of Deiters' nucleus (No. 113, figs. 3*a* and 3*b*, and No. 118), and one with an extensive sagittal lesion lateral to the left posterior longitudinal bundle, and cutting Deiters' complex from the raphe (No. 158, fig. 10). In all three cases we find a degeneration undoubtedly of the same ascending bundle which we described in §§ 1 and 2. The area of the degeneration is exactly the same; it is here found on the side opposite the lesion. The crossing over of the fibres is visible between the level of the distal end of the triangular part of Deiters' nucleus (Fuse) and the decussation of the fourth nerve. This ascending degeneration is more extensive in No. 113 (fig. 3*b*), where the entire triangular part of Deiters' nucleus is cut through, than in No. 118, where it is principally the dorsal large-celled part of the nucleus which is injured. From this we may infer that the crossed vestibulo-mesencephalic bundle originates more especially in the triangular ventral part of the nucleus of Deiters.

Besides this compact bundle on the opposite side, there is a less compact bundle degenerated on the side of the lesion. This ascends in the extreme lateral part of the posterior longitudinal bundle formation (Winkler's fasciculus Deiters ascendens). In No. 158, however, the homolateral ascending degeneration is differently situated. The significance of this ascending degeneration will be considered in Chapter III, §§ 4 and 5.

A comparison of No. 113 with No. 118 affords us a special opportunity of determining more exactly the origin of the direct vestibulo-spinal bundle. In No. 118 (lesion of Deiters' nucleus in the narrower sense) this bundle is completely degenerated, although the lesion is limited; in No. 113 (lesion of the triangular part) there is far less degeneration. From this we may conclude that the direct vestibulo-spinal bundle originates more particularly in Deiters' nucleus in the narrower sense, and this agrees with v. Monakow's original

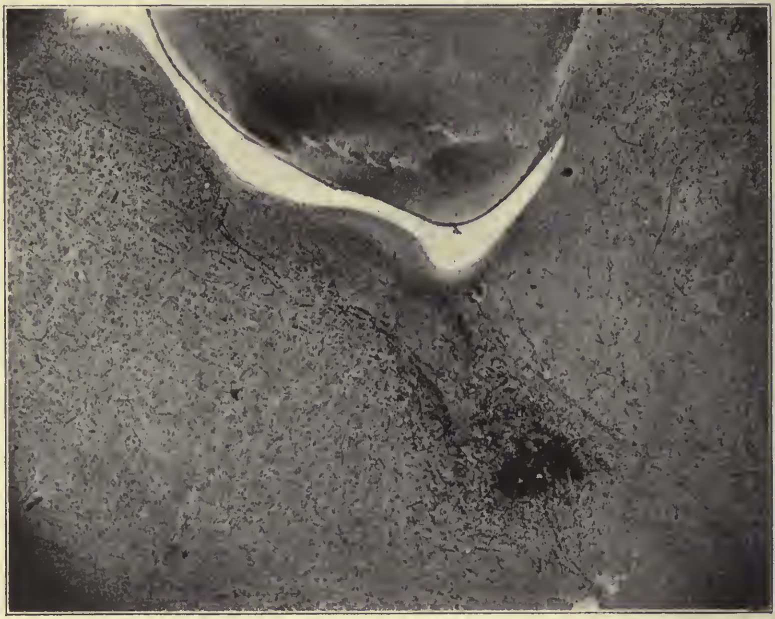

Fig. 3*a*.

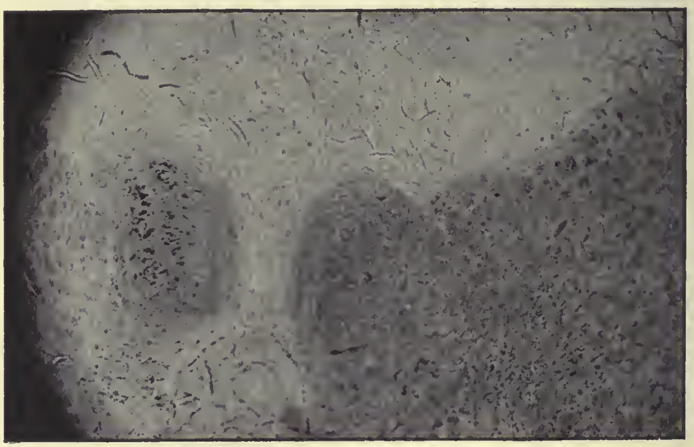

Fig. 3*b*.

FIGS. 3*a*, 3*b*.—Cross sections of cat 113.

Fig. 3*a*.—Stab through Deiters' nucleus.
Fig. 3*b*.—Ascending degenerations in the upper pontine region.

description, and with the findings of Ferrier and Turner, Risien Russell, Thomas, and others.

A descending degeneration in the fibres of the posterior longitudinal bundle also is found on the side of the lesion in any case (particularly after lesion of Deiters' nucleus in the narrower sense). The situation of this homolateral, vestibulo-spinal bundle in the spinal cord is more dorsal and lateral than that of the corresponding crossed bundle. In the region of the cord its fibres intermingle with those of the direct dorsal vestibulo-spinal bundle just described, and which in these cases is also degenerated. This intermingling of the two homolateral descending bundles, their mutual origin from Deiters' nucleus in the narrower sense, and the fact that everywhere in the medulla oblongata degenerated fibres are found, which occupy the intervening space between their two areas, lead us to suppose that these two bundles are identical, both genetically and functionally.

As regards these *homolateral vestibulo-posterior longitudinal bundle-fibres* of Probst, van Gehuchten, and others, I would agree with Thomas and van Gehuchten, that in lesions in the region of Deiters' nucleus one is constantly struck by the great and apparently fundamental differences in the descending degenerations found.[1]

This may be due to the peculiar shape the lesion takes, but it may also be due to the circumstance that Deiters' nucleus, as Kohnstamm has mentioned, is composed of cells of various sizes, which possibly do not all suffer in the like degree from a lesion in this region. Something similar is found in regard to the different bundles of the posterior longitudinal bundle formation, which do not suffer equally when the posterior longitudinal bundle passes through a softened area, for some of the fasciculæ degenerate, and others remain intact [108]. In the same way differences appear to occur in different species in the relative position of the descending bundles, which has led even van Gehuchten to suppose that in the rabbit the homolateral descending vestibular fibres in the posterior longitudinal bundle are missing.

The situation of the homolateral descending Deiters' fibres in the spinal region of the longitudinal bundle is about the same as that of the descending homolateral degeneration, after incision of one posterior longitudinal bundle in the pons region (Chapter I, § 1). In some cases, however, we find the Deiters' fibres more dorsally situated. This fact, coupled with our observations to be referred to presently in regard to the heterolateral descending bundle, makes us question whether it is possible to determine which part of the descending fibres originates in the reticular cells in the region of Deiters' nucleus, and which part in Deiters' nucleus proper. This may be determined possibly by the application of Clarke and Horsley's method of localized lesion. Lewandowsky declared that it was impossible to define Deiters' nucleus sharply from the cells of the reticular formation. The observations of Kohnstamm and Lloyd, however valuable in other respects, did not bring conclusive evidence to bear upon this subject.

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[1] To give a typical example, I would refer to cat No. 7, of Lewandowsky. From the character and situation of the ascending degenerations (both exclusively on the same side as the lesion, cf. § 5 of this Chapter) in the posterior longitudinal bundle formation, there seems to be no doubt that Bechterew's nucleus is affected. Nevertheless one still finds in this case of limited lesion of the *oral* part of the vestibular region the direct vestibulo-spinal bundle considerably degenerated.

Generally speaking, we may say that the course of the crossed ascending vestibulo-mesencephalic bundle, of the direct vestibulo-spinal bundle, and of the homolateral descending bundle in the posterior longitudinal bundle formation, after lesion of Deiters' nucleus, as described by the first authors upon this subject (Held, Ferrier, Turner, Russell, and Thomas), corresponds with the results of the later investigators just mentioned and also with my own, save for the data in regard to the reticulo- or ponto-spinal fibres.

Heterolateral descending bundles from Deiters' nucleus. — This matter we shall have to discuss at some length, since opinions differ regarding it.

The cause of these differences of opinion, as far as I can see, is due to the variety of methods adopted in operating, and to the fact that it is not generally recognized that there exist marked anatomical and physiological differences amongst secondary connexions of the different parts of Deiters' nucleus, a circumstance which complicates their analysis very much.

Although we are much indebted to the investigations of Probst, Winkler, and Lewandowsky for our present knowledge of this region, the extensive lesions made by these experimenters cause such widespread degeneration that one is scarcely warranted in drawing definite conclusions in regard to these bundles. Fraser [59] avoids this difficulty by first severing the occipito-atlantal ligament and then incising the most distal parts of Deiters' region with a pointed galvano-cautery. Van Gehuchten experimented with rabbits, and injured, to judge from his figures, the caudal part of the vestibular region, by extracting the facial nerve. Probst's and my own lesions were made by means of a concealed needle piercing the cerebellum; as Horsley and Clarke have definitely shown that neither from the cortex cerebelli, nor from the intrinsic nuclei do any fibres degenerate directly in the spinal cord, this method seems the most suitable for our purpose.

Wallenberg experimented on pigeons. Although his observations are models of clearness, yet the great disadvantage of experiments upon these birds is the minute extent of the relative parts, so that any advance in the differentiation of the various parts of the vestibular nuclei is not likely from them.

We owe our knowledge to von Monakow and Kohnstamm, and above all to Probst and van Gehuchten that, in addition to a homolateral bundle, there exists also a crossed ponto-spinal or reticulo-spinal bundle, which descends in the area of the posterior longitudinal bundle.

It appears to me that the degeneration of this bundle has interfered to an extraordinary degree with the analysis of numerous experiments, because of the peculiar and capricious shape of its field of origin (Kohnstamm). Thus, for example, I find it degenerated in No. 139 (fig. 1*c*), where there was a sharply defined lesion of the mesial part of the posterior longitudinal bundle (fig. 1*a*), and from this and other experiments I have come to the conclusion that the ganglion-cells for this tract must be present undoubtedly in the immediate vicinity of the posterior longitudinal bundle from below the exit of the sixth nerve (cf. Fraser's monkey, A 2) up to the posterior corpora quadrigemina.

I have shown (No. 93, fig. 5*c*, and No. 95, § 5) that subsequent to a lesion limited to Bechterew's nucleus, there is no crossed descending degeneration of posterior longitudinal bundle fibres, and although in lesions such as those of van Gehuchten's experiments, where the distal part of Deiters' nucleus was involved, there was such degeneration, I do not consider, as I have said, that such experiments can be regarded as conclusive and do not feel justified therefore in assuming with Fraser, Winkler and van Gehuchten, that Deiters' nucleus regularly possesses a crossed descending connexion with the posterior longitudinal bundle. In many cases of lesion of Deiters' nucleus the direct vestibulo-spinal bundle, and also the homolateral Deiters' posterior longitudinal bundle fibres are degenerated, but crossed fibres are lacking, and until some further advance has taken place in our knowledge of the anatomical and physiological relations of this region it is impossible to decide whether any part of Deiters' nucleus, much less what part, gives rise to heterolateral descending fibres.

§ 4.—*Lesion of the Mesial part of the Lateral Horn of the Posterior Longitudinal Bundle (Homolateral Vestibulo-mesencephalic Bundle) (Table I, Group* 4, *p.* 376).

In one cat with a lesion low down in the pons region, the larger fibres of the crossed vestibulo-mesencephalic bundle remained intact, but an area lateral to this bundle was degenerated on the side of the lesion (No. 68).

This case appears especially interesting from the fact that hæmorrhage took place exactly in the area of the posterior longitudinal bundle (fig. 4); in this animal there was noted a circus movement, or rather a maximal conjugate deviation of head, neck and eyes to the non-operated side, for thirteen days.

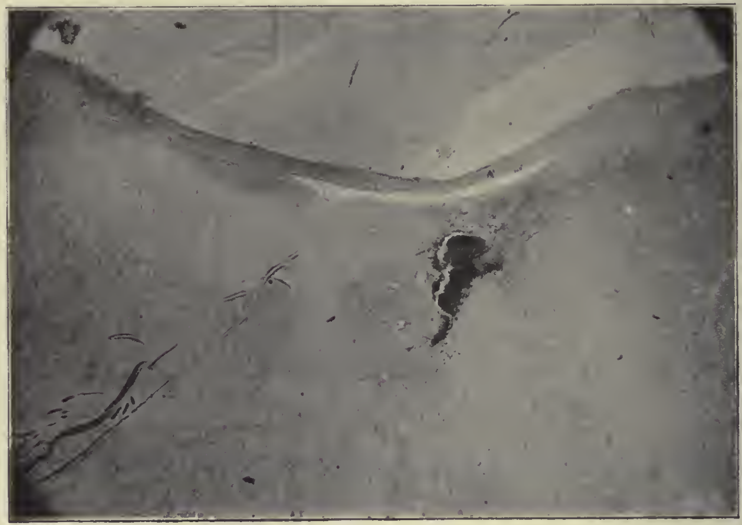

FIG. 4.—Lesion (hæmorrhage) in lateral horn of posterior longitudinal bundle of cat 68.

These degenerated fibres may belong to the area of the crossed vestibulo-mesencephalic bundle; however, Deiters' nucleus of the other side is intact; no descending degenerated fibres in the posterior longitudinal bundle were present except on the side of the lesion and these were situated dorsally and laterally and the direct vestibulo-spinal bundle was not degenerated; moreover, the fibres were of more delicate structure than those of the crossed vestibulo-mesencephalic bundle and were situated more laterally in the posterior longitudinal bundle formation. It seemed, therefore, likely that these degenerated fibres might have a different origin from that of the crossed vestibulo-mesencephalic bundle.

§ 5.—*Lesion of Bechterew's Nucleus* (*Table I, Group* 5, *p.* 376).

This supposition was strengthened as soon as we examined two animals that had sustained a lesion limited to the situation of Bechterew's nucleus (No. 93, figs. *5a*, *5b*, *5c*, *5d*, and No. 95, figs. *6a*, *6b*). In these we found this ascending bundle, and also a bundle of fibres descending in the spinal part of the posterior longitudinal bundle degenerated, but only on the side of the lesion. The origin of this ascending bundle could hardly be other than Bechterew's nucleus. It is then a homolateral vestibulo-mesencephalic bundle (as described by Wallenberg, Winkler and van Gehuchten) which ascends in the direction of the posterior commissure.

The physiological significance of this homolateral ascending bundle which pursues its course lateral to the crossed vestibulo-mesencephalic bundle, appeared closely connected with that of the crossed bundle. This is probable from the fact that animals in which one of these bundles (crossed or uncrossed) was degenerated performed circus movements to the healthy side (*cf.* §§ 1 and 3 of this chapter), or else conjugate deviation of head and eyes (fig. *5d*) was present.

The homolateral descending fibres of Bechterew's nucleus (less in number in cat 95, where Deiters' nucleus was entirely intact) occupy a more dorsal and lateral position in the spinal part of the posterior longitudinal bundle formation than do the descending homolateral fibres from Deiters' nucleus.

CHAPTER II.—A CENTRIFUGAL BUNDLE IN THE POSTERIOR LONGITUDINAL BUNDLE-FORMATION WHICH CONTROLS CIRCUS MOVEMENT TO THE SIDE OF THE LESION.

Up till now we have become acquainted with two vestibulo-mesencephalic bundles, the mesial one of which is crossed and ascends from the ventral triangular part of Deiters' nucleus, while the lateral one ascends uncrossed from Bechterew's nucleus. The ascending degeneration of either of these tracts and the associated descending degenerations in the spinal part of the posterior longitudinal bundle are apparently always accompanied by circus movements or with conjugate deviation of head and eyes to the non-degenerated side. We

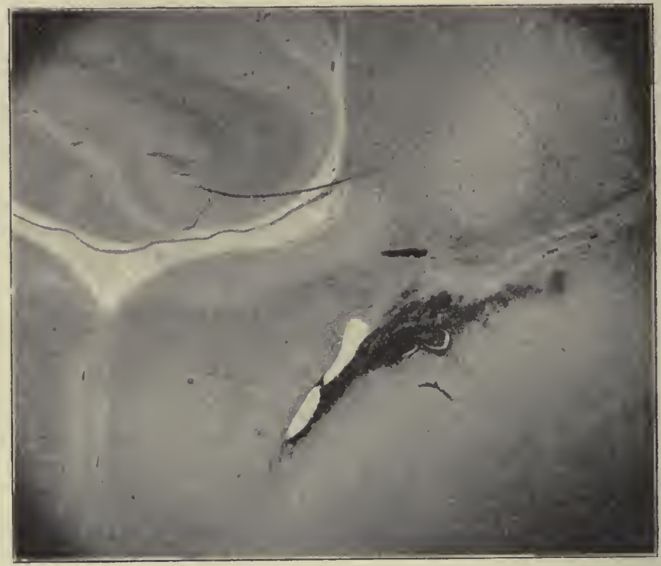

Fig. 5*a*.

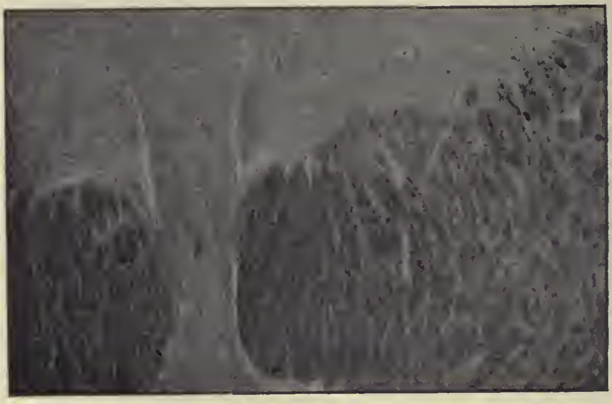

Fig. 5*b*.

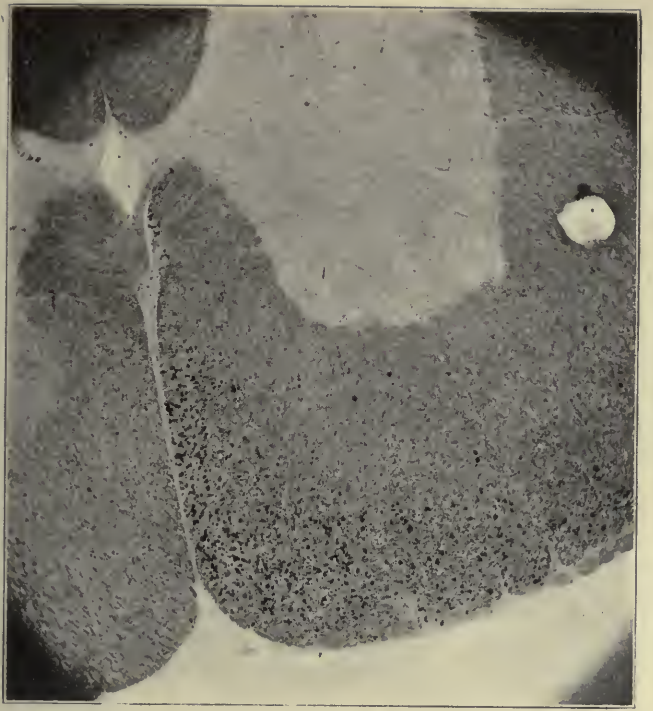

Fig. 5c.

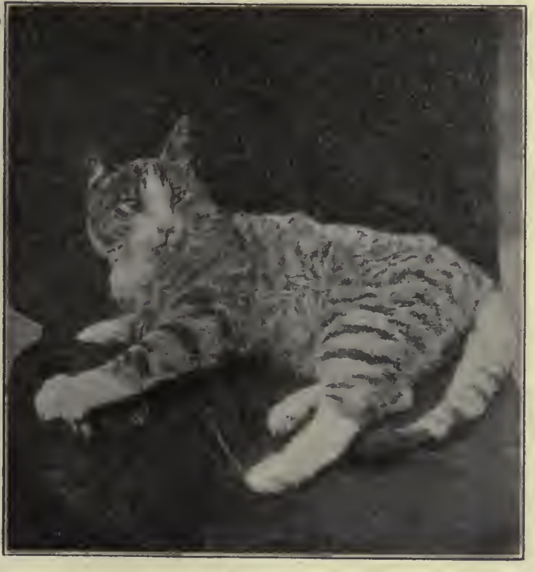

Fig. 5d.

Figs. 5*a*, 5*b*, 5*c*, 5*d*.—Taken from cat 93.

Fig. 5*a*.—Lesion in the region of Bechterew's nucleus.

Fig. 5*b*.—Ascending degeneration in the mesial part of the lateral horn of the posterior longitudinal bundle in the upper pontine region.

Fig. 5*c*.—Descending degeneration in the upper dorsal region of spinal cord.

Fig. 5*d*.—Photograph of cat 93, taken thirteen days after operation. Note conjugate deviation of head and eyes towards the left side.

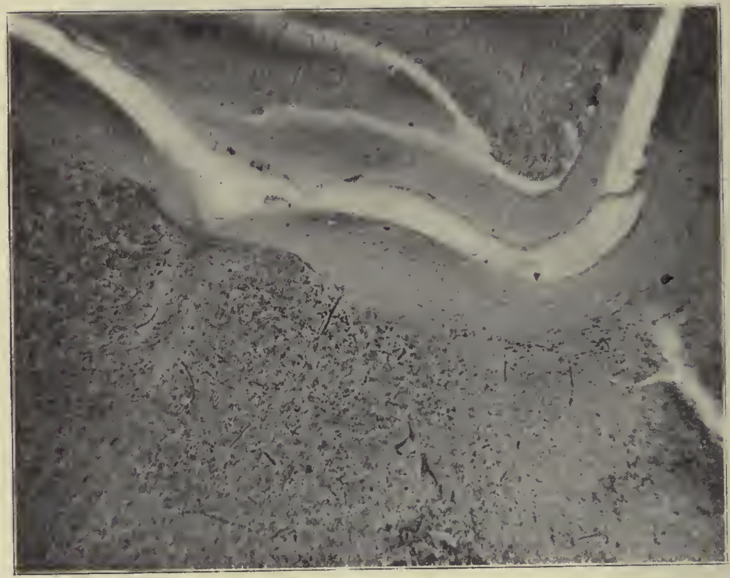

Fig. 6*a*.

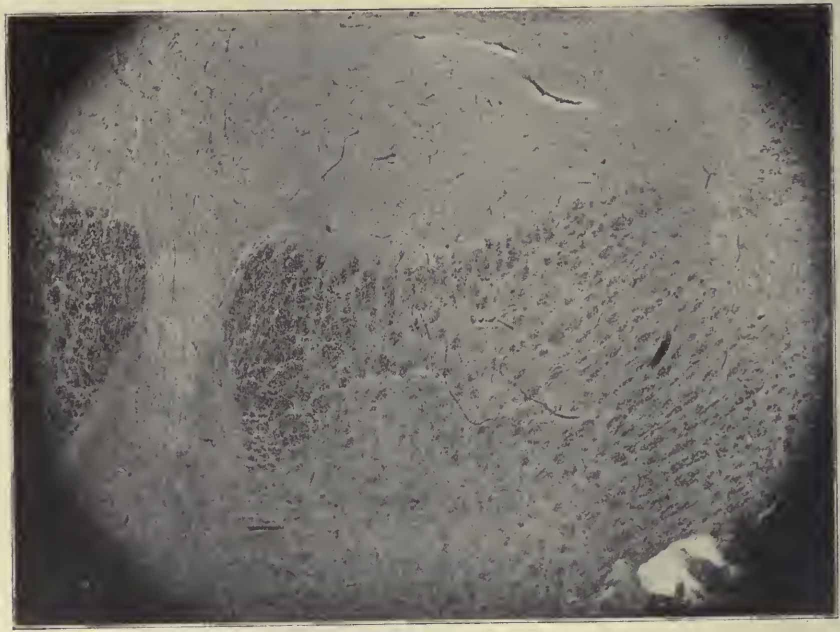

Fig. 6*b*.

Figs. 6*a*, 6*b*.—Cross sections of cat 95.

Fig. 6*a*.—Lesion in the region of Bechterew's nucleus.
Fig. 6*b*.—Ascending degeneration in the upper pontine region.

have now to determine, therefore, whether our experiments afford any support for the theory, so constantly advanced by recognized authorities, that the posterior longitudinal bundle and its connexions should be looked upon as the pathway of the reflex mechanism for the maintenance of equilibrium. This supposition has been discussed by Edinger, Bleuler, R. Russell, v. Bechterew and Wallenberg, and has been definitely accepted as correct by Spitzer and Kohnstamm. From a clinical point of view, arguments in support of it have been advanced by Prévost, v. Monakow, Spitzka, Gowers, Gee, Tooth, Kaplan, Finklenburg, and others, and these have been accepted on anatomical grounds by Bielschowsky, Bertelse and Rönne, and Lewandowsky. We would consider it our duty, therefore, to examine specially our present material, in order to determine whether it justifies us in dismissing the idea as purely hypothetical, or whether it contributes any definite experimental proof in support of this theory which has been arrived at by such a variety of physiological, pathological and clinical means. It would be a strong argument for the conception of the posterior longitudinal bundle as a pathway for the mechanism of the equilibrium of motion in the horizontal plane, if we were to find that the bundle also contains fibres, the descending degeneration of which is associated almost constantly with circus movements.

With this object in view, we naturally turn our attention to the region where our ascending bundles terminate, and which is obviously closely connected with forced movements, namely, the region of the posterior commissure. We must first determine, therefore, what are the physiological and anatomical consequences of a lesion in this region, and then particularly look for the descending degenerations in the posterior longitudinal bundle, consequent to those lesions, that were associated with circus movements.[1]

For this purpose we have at our disposal seven of my own experiments (Nos. 107, 108, 106, 109, 98, 61, Table II, Group 10, p. 378).

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[1] The origin and termination of two descending bundles had already been recognized by myself for some time, and they had been termed fasciculus commissuro-medullaris and fasciculus interstitio-spinalis, not only in my article in the *Nederl. Koninklijke Academie* of October and November, 1912, but also in the manuscript which I sent in December, 1912, to the editor of *Neuraxe*, together with a table and rough outlines of the results of twenty-five experiments; these latter only were published in that journal. My communication concerning circus movements was published in the *Neuraxe* of January, 1914. Since then v. d. Schueren has confirmed the existence of the commissuro-medullary and interstitio-spinal bundle (*Neuraxe*, May, 1913).

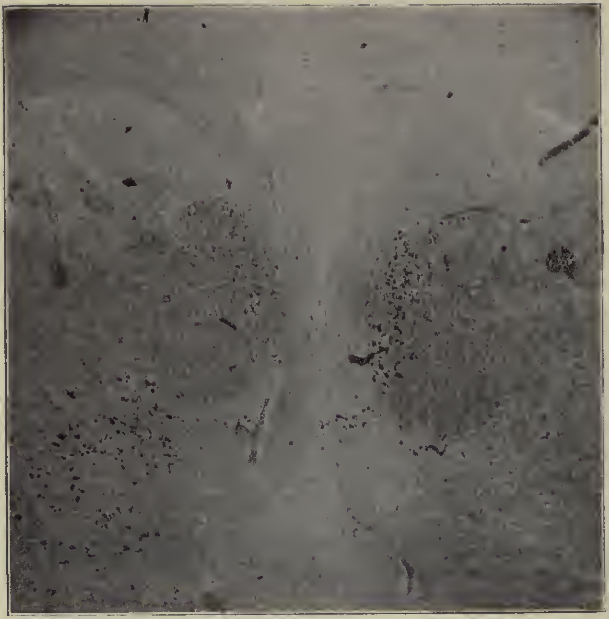


Fig. 7*a*.

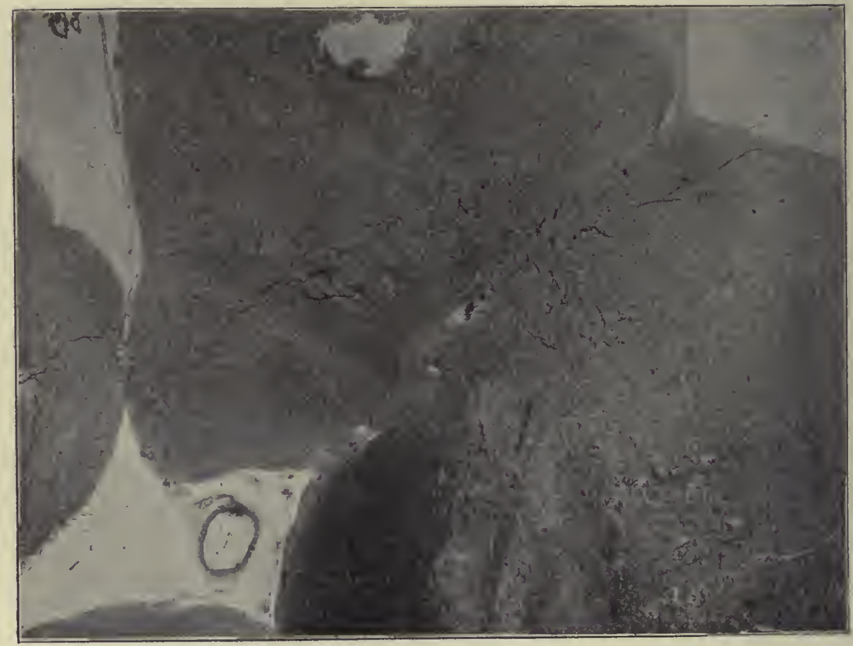


Fig. 7*b*.

Figs. 7*a*, 7*b*.—Cross sections of cat 108.

Fig. 7*a*.—Descending degenerations in the posterior longitudinal bundles in the region of the trochlear nucleus. Note on the right side the coarse-fibred tractus interstitio-spinalis, on the left the fine-fibred tractus commissuro-medullaris.

Fig. 7*b*.—Descending degenerations in the medulla oblongata. Note on the right side presence of coarse-fibred fibres; no degeneration on the left.

By reference to Table II we notice that, again in accordance with the law of Schiff and Probst ("a hemisection in the caudal parts of the optic thalamus causes circus movements to the side of the operation"), five of these animals executed circus movements to the side of operation for longer or shorter periods. Cat No. 108 was an exception, as it performed rolling movements to the left side or side of operation for a very unusual length of time and circus movement to the left side for one day only. This case exhibited an extraordinary localization of the lesion, which caused degeneration of the commissuro-medullary bundle on the left, and of the interstitio-spinal bundle on the right side (figs. 7*a*, 7*b*).

In this connexion we would recall that in the year 1881 v. Bechterew had already noted circus and rolling movements after lesion of this region; these he afterwards described in detail [11]. Lewandowsky [89] (p. 137), obtained similar results. Both these writers remark, and rightly, that these movements are never characterized by the vehemence which so regularly occurs after lesion of the vestibular region.

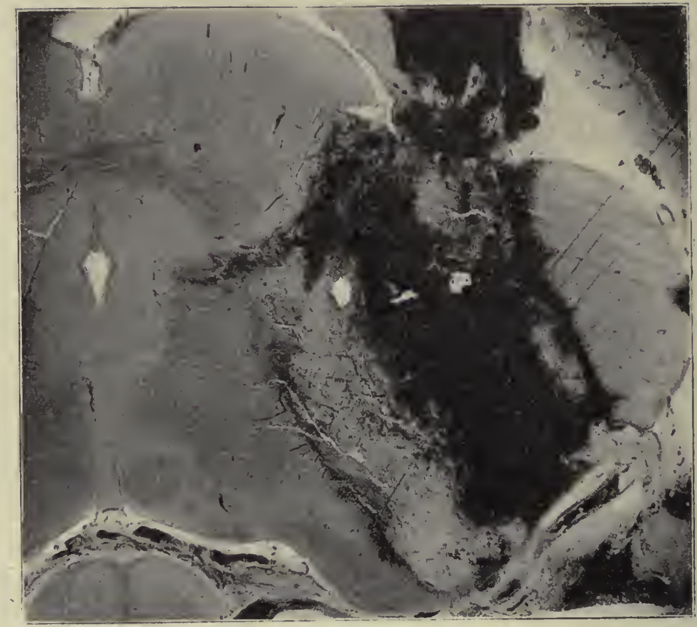
A delicately granuled tract was found more or less degenerated in all these five animals, on the side of the lesion, in the mesial part of the posterior longitudinal bundle. In No. 61 it was on both sides of the middle line as the results of the bilateral character of the lesion.

Before proceeding to correlate the anatomical data and the physiological consequences observed, we must exclude any accidental injury of the vestibular nerve, as even limited lesions in its area are so peculiarly liable to bring about forced movements (*cf.* Chapter III, §§ 1, 2, & 3).

In No. 106, for example, we find the nervus vestibularis on the left side slightly speckled with black dots, a condition similar to what was observed in No. 61. If, however, we remember that a lesion of this nerve invariably produces rolling movements to the side of the lesion, we can safely set aside the objection that the circus movements to the right and the left in this group of animals which we are considering, were due to an indirect lesion of the nerve root. It is also unlikely that the slight speckling of the two vestibular nerves (equally) in No. 108, could cause the prolonged tendency to fall to the left side. In No. 109 numerous delicate black granules were found in the two Deiters' nuclei, and as regards this animal we cannot say positively that the circus movement to the right for one whole day was not owing to this unintentional indirect lesion of Deiters' nuclei.

In regard to five animals then, we have notes of the duration and the nature of the forced movements, and also of the different

Left.



Right.

Fig. 8*a*.

Left.

Right.

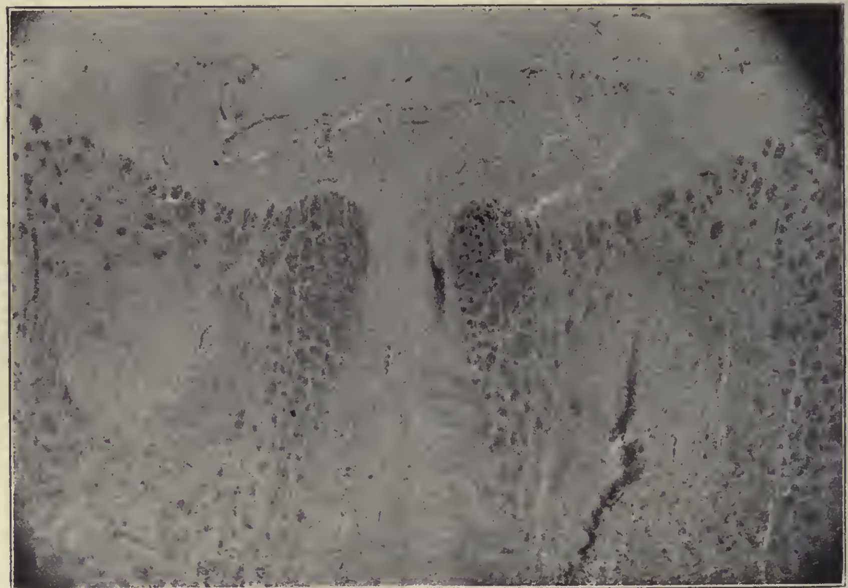


Fig. 8*b*.

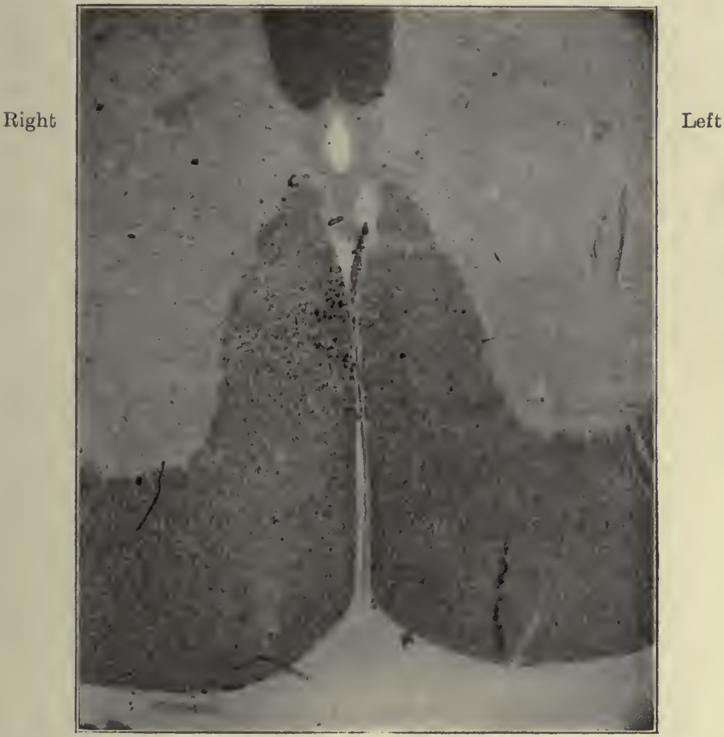


Fig. 8*c*.
FIG. 8*a*, 8*b*, 8*c*.—Cross sections of cat 107.

Fig. 8*a*.—Extent of the lesion at the level of the anterior quadrigeminate body.
Fig. 8*b*.—Level of the nucleus tegmenti profundus. Note the coarse-fibred tractus interstitio-spinalis on the side of the lesion.
Fig. 8*c*.— This same tract in the dorsal region of the spinal cord, on the side of the lesion (by mistake sides reversed).

descending degenerations in the area of the posterior longitudinal bundle, which may possibly be responsible for these movements. The bundle lateral to the posterior longitudinal bundle, as described by Probst, Economo and Karplus, was found degenerated only in Nos. 106 and 108, and was perfectly intact in Nos. 107 and 61, which animals executed distinct circus and rolling movements. From the hypothesis we have mentioned, and which regards the posterior longitudinal bundle as the pathway of a reflex mechanism, we may suppose that there exists a centrifugal component controlling the circus movement. We must investigate, therefore, the condition of the descending tracts within the posterior longitudinal bundle, the lateral bundle having probably nothing to do with these movements.

These descending mesencephalic fibres in the posterior longitudinal bundle, already noted by Held, have been examined after the Marchi method and described by Boyce, Redlich, and Probst in mammals. In them, however, we have to deal with a double bundle, the component parts of which begin and end differently. Their different course was first described in the year 1912 [108], and the bundles were termed the commissuro-medullary and interstitio-spinal bundle. Cajal, Wallenberg, and van Gehuchten discovered the descending mesencephalic fibres of this region in birds and fishes. De Lange studied them in different species of animals, and considered them homologous with the uncrossed tecto-bulbar bundle of the fish. In a rabbit he followed them right into the sacral region. As regards man, centrifugal fibres in the posterior longitudinal bundle have been described by Gee, Tooth and Roussy as being situated in its mesial segment, and, according to Roussy, also in its dorsal part.

Where we can follow this part of the posterior longitudinal bundle in its downward course as in Nos. 107 and 108, we can readily determine that we have before us here two separate anatomical entities; in No. 107 we can follow the interstitio-spinal bundle as a separate strand of coarse fibres well into the lumbar region of the spinal cord (fig. 8*c*). It is situated in the anterior column and runs close to the anterior fissure, about two-thirds of the way from the ventral to the dorsal end of the fissure. On the other hand, in No. 108 we see that the delicately fibred tract on the left side (fig. 7*a*), most mesially situated in the posterior longitudinal bundle, disappears caudally in the abducens nucleus in the oblongata (fig. 7*b*), and only a few solitary fibres from it can be followed into the cervical spinal cord, or lower.

When we now consider (Table II) that in unilateral lesions of the region of the posterior commissure, which are followed by circus movements to the side of the lesion, with conjugate deviation of the head and eyes, we constantly find degenerated fibres in the innermost part of the posterior longitudinal bundle, descending towards the medulla, it thus seems likely that we have here the centrifugal limb of the reflex arc which controls circus movements to the side of the mesencephalic lesion.

We must conclude therefore that in the posterior longitudinal bundle there are found not only two tracts on each side of ascending fibres, the degeneration of which occurs simultaneously with circus movements to the healthy side, but also on each side a centrifugal "final common path" [Sherrington 147], the descending degeneration of which is associated with circus movements to the side of the lesion. In agreement with this theory of Sherrington's is the circumstance that the ascending fibres of this reflex arc are much more abundant than the descending. The condition resembles that of the single giant Mauthner-fibre of fishes, which, according to Kohnstamm, controls the motion of the tail fin.

None of my experiments is in direct opposition to this supposition; one of Economo and Karplus's experiments also (referred to in Table II) may be regarded as supporting it, and Roussy's [135] results and Kohnstamm's may be interpreted also as in agreement with it.

It is true that I find in some of my thalamic lesions in certain animals the same phenomena as were present in cat No. 1 of Roussy's series. This animal, although the nucleus of the posterior commissure and the commissuro-medullary bundle were intact, performed circus movements towards the operated side for some time. But in Chapter VI this class of experiments will be dealt with especially, i.e., lesions of a tract of fibres that connects the cerebral hemisphere (striate body) with the region of the posterior commissure. To declare, as Roussy does, the degree of circus movement to be in proportion to the injury of the pedunculi, would be neither in accordance with my own results, nor with those of other authors, Roussy's included.

Direct electric stimulation of this region may contribute towards the ultimate solution of this anatomo-physiological problem. This question also will be taken up further in Chapter VI.

CHAPTER III.—THE PRIMARY AND SECONDARY VESTIBULAR CONNEXIONS, AND FORCED MOVEMENTS IN THE PLANE VERTICAL TO THE LONGITUDINAL AXIS OF THE ANIMAL (ROLLING MOVEMENTS).

§ 1.—*Lesion of the Vestibular Root* (*Table I, Group 6, p. 376*).

In Group 6 of Table I we have included those cases in which the vestibular root itself was injured by the instrument, or was found degenerated to such an extent that some indirect injury to it must have taken place by stretching, or hæmorrhage, or in some such way.

The forced movements after direct lesion of the vestibular root, that is to say in the cases with definitely confirmed total degeneration in the nerve-root, are of far longer duration than those after indirect lesions or

TABLE I.—CENTRIPETAL TRACTS IN

Experiment	Lesion	Duration of life	Circus movement
	Group I.—Section of the median part of the bundle on one side. (Compare		
139	In middle pontine region, on right side	15 days	To the left ..
119	Region of posterior corpus quadrigeminum, on left side	7 ,,	To the right ..
91	Lower pontine region, on left side	16 ,,	,, ,, ..
	Group II.—Section of median part of bundle on both sides.		
114	Oral to 4th nucleus	21 days	—
97	,, ,, ...	6 ,,	—
92	Both bundles and left lateral horn, in lower pontine region	14 ,,	Head deviated to right side
90	Both bundles and right lateral horn, in lower pontine region	21 ,,	To right side, with conjugate deviation of head and eyes
	Group III.—Lesions of different		
113	Nucleus Deiters (triangular part), on right side ..	20 days	To the right ..
118	Nucleus Deiters proper on right side	28 ,,	,, ,, (?) ..
158	Sagittal lesion, cutting off vestibular region from raphe, on left side	15 ,,	To the left ..
	Group IV.—Lesion of the homolateral		
68	Softening of lateral part of pons ; hæmorrhage in lateral horn, on right side	14 days	Maximal conjugate deviation to left
	Group V.—Lesions of		
93	Bechterew's nucleus and dorsal part of crus cerebelli ant., on right side	28 days	Tendency to walk to left
95	Bechterew's nucleus and nucleus brachii pontis sup., on right side	24 ,,	To the left ..
	Group VI.—Lesion		
23.5.00	Acustico-vestibular region, on right side	28 days	Head turned to right
Rabbit V	Extirpation of so-called flocculus, on right side ..	11 ,,	—
42	Acustico-vestibular exit, on right side	33 ,,	—
67	Destruction of nucleus vestibularis and ganglion ventrale, on right side	20 ,,	—
	Group VII.—Lesion of Ramus		
VIII	Cyst in caudal part of ram. desc. viii, on right side	34 days	—
18	Flocculus cerebelli, corpus restiforme, and ram. desc., on right side	11 ,,	To the right ..
35	Corpus restiforme, nucleus desc. v and viii, softened, on left side	34 ,,	—
146	Sagittal lesion through caudal part of corpus trapezoides, on right side	13 ,,	Tendency to walk to left
158	Compare Group III.		
	Group VIII.—Lesion of Deiters' nucleus.		
	Group IX.—Lesion of lateral horn of posterior longitudinal bundle. (Compare Group		
62	Incision in crus cerebelli ant., and lateral horn, on right side	14 days	—
150	Lesion of lateral part of lateral horn, on right side	15 ,,	—
221	Two punctures through lateral horn, on left side ..	14 ,,	Head bent to left(?)
	Group X.—Lesion of median part of lateral horn of posterior longitudinal No. 158, and Cat 5		

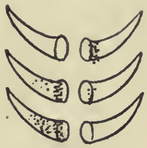
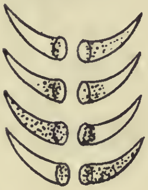
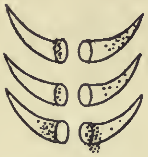
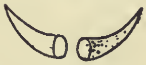
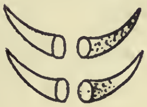
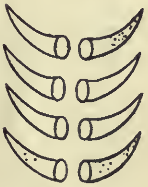
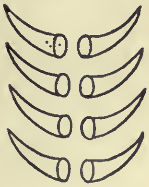
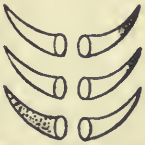
Duration	Rolling movement	Duration of movement	Area of P.L.B. to 4th nucleus
Probst's Case IX [123, p. 72] and Economo's Case V [78, p. 411].)			
10 days	.. ..	—	
2 ,,	.. ..	—	
8 ,,	Falls on right; lies down on right side ..	14 days	
(Compare Fraser's Monkey No. 2 [59, p. 383].)			
—	Staggers	—	
—	"Tumbling"; falls to left and right.. ..	5 days	
4 days	Falls to left; eyes rotated to left	4 days; 12 days	
9 ,,	Head rotated to right	2 days	
parts of Deiters' nucleus.			
8 days	Head rotated to right	8 days	
1 day	Falls to right	7 ,,	
9 days	,, ,, ...	11 ,,	
vestibulo-mesencephalic bundle.			
10 days	Lies on left side..	Few days	
Bechterew's nucleus.			
6 days	Rolls to right; falls to right	8 days; 22 days	
5 ,,	.. ..	—	
of vestibular root.			
25 days	Rolls and falls to right; lies on right side	28 days	
—	Head rotated and bent to left	11 ,,	
—	Vehement rolling to right; rotation of eyes	33 ,,	
—	,, ,, ,, ,, ,,	20 ,,	
descendens nuclei vestibularis.			
—	Rolls to left; head and eyes rotated to left	2 days; 4 days	
3 days	Rolls to left	3 days	
—	Tendency to roll to right	12 ,,	
Some days	Slight tendency to roll to left	Some days	
(Compare Group III, Nos. 113 and 118.)			
II, Nos. 90 and 92; Group V, No. 93, and Kohnstamm's Rabbit IV [81].)			
—	Rolls to right	6 days	
—	,, ,, ...	5 ,,	
1 day	Lies down exclusively on left side	3 ,,	
bundle. (Compare Group I, No. 91; Group IV, No. 68; Group VII, of Karplus [78].)			

TABLE II.—CENTRIFUGAL TRACTS IN

Experiment	Lesion	Duration of life	Fasc. commissuro-medullaris	Circus movement
107	Lesion of lateral part of posterior commissure (middle division), on right side	11 days	Degenerated on right side	To the right
108	Region antero-lateral to red nucleus, on right side	18 ,,	Degenerated on left side	To the left
106	Extreme antero-lateral part of posterior commissure, on right side	21 ,,	Few fibres, right > left	—
109	Extreme oral part of posterior commissure, on right side	17 ,,	,, ,,	Tendency to walk to right
98	Lesion of latero-posterior part of posterior commissure, on right side	19 ,,	Degenerated on right side	To the right
61	Region of posterior commissure, on right and left sides	26 ,,	Left > right..	Tendency to walk to left

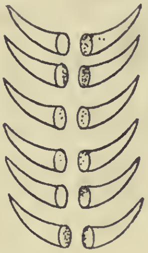
Compare also Probst's Case [123, p. 527], Besta's Cat [17, p. 417],

than the forced movements described in the first two chapters of this paper. Also the character of the rolling associated as a rule with the Hertwig-Magendie squint (the eyeball of the side of the lesion being deviated downward, that of the other side being directed upward) is far more vehement in the case of a direct root lesion. In cats it is only after direct injury of the vestibular nerve that rolling movements continue for weeks; after secondary or indirect lesions of the vestibular nerve, and *a fortiori* after lesion of the ascending systems only, minor phases only of forced movements were noticed, such as a tendency to lie on one side, to fall to one side, or a rotation of the head to one side, when the chin was moved away from the direction of the rolling.

As soon as the anæsthesia passes off in lesions of the vestibular root, there occurs usually a rotation of the eyeballs on their antero-posterior axis towards the side of the lesion, a rotation which is easily demonstrated in cats because of the slit-like shape of the pupil, and in rabbits can be made apparent by the performance of a preliminary iridectomy [107]. The upper half of both eyeballs is seen to be rotated towards the side of the lesion, the lower half from the side of the lesion. Further nystagmoid movements of the eyeballs can be observed, slow in character in the direction of the rotation, but rapid in character in the opposite direction. This rotatory nystagmus usually lasts for a few days only, and is increased by turning the head in the direction *opposite* to that of the rotation.

After compensation of the rolling movements has taken place, they may be renewed by blindfolding the animal. For a long time

POSTERIOR LONGITUDINAL BUNDLE.

Duration	Fasc. interstitio-spinalis	Rolling movements	Duration of movements	Area of P.L.B.
8 days	Degenerated on right side	Head rotated to left side	8 days	
1 day	Degenerated on right side	Tendency to fall on left side	9 ,,	
—	—	.. ..	—	
Few hours	Few fibres (?)..	.. ..	—	
1 day	Few fibres on left > right	Slow rotatory jerks to right side	Few hours	
3 days	—	Slight tendency to roll to right side	3 days	

and Karplus's Cat 3 and Macacus 3 [78, pp. 298 and 342].

the animal can also be pressed down more easily to the side to which he tended to roll than to the other side. By Marey's falling experiment (the normal cat on being taken up by its legs, and dropped, invariably lands upon its paws) the rolling can be brought about again, and in epileptic fits it may also recur. It is remarkable, however, that in ether narcosis a rotation in the opposite direction [137, cf. also 133] is observed.

In studying this group of animals (Group 6) we notice that, with the exception of rabbit V, the rolling movements invariably occurred in such a manner that the locomotion was always to the side of the injured vestibular nerve. This accords with the earlier experiments of Flourens, Schiff and Cyon, and with those of Ewald, Breuer, Winkler, Camis, Bartels, and others of later date, dealing with lesions of the semicircular canals and section of the nervus acustico-vestibularis.

It is outside the province of this paper to discuss the hydrokinetic theory of these organs, simultaneously brought forward by Crum Brown, Breuer and Mach, or to recall the extensive literature concerned with stimulation experiments performed upon the semicircular canals and the acoustic maculæ. I will merely remark that a lesion of one canal tends to produce deviation or movement in the plane of that canal as well as corresponding alterations in the compensatory changes in position of the eyeballs that take place during movements of the body [31, 70, 84, 87] (pathological observations of Stein, Stenger, Bourgois, Bezold, van Uffenorde). It is well known that not only in vertebrates, but also in invertebrates, for example in octopods (v. Uexkull, Muskens [110] Prentiss), removal of the whole otolitic organ invariably causes rolling movements to the side of the lesion, together with corresponding disturbance of independently moving parts of the body (eyeballs, fins, tail, &c. [18, 93]).

As regards the more recent researches concerning the vestibular nerve itself, I would quote those of Biehl [21], relating to direct electrical stimulation of this nerve in horses and sheep. During the stimulation, for instance, of the right nerve, a deviation was observed of both eyes to the right side, with small rapid nystagmus in the same direction; at the same time there was a squint present, the left eye being below, the right above, a deviation which is found in animals that roll to the left side. Immediately after severance of the vestibular nerve, on the other hand, the deviation of the eyeballs and the squinting were in exactly the opposite direction; thus, after section of the right root, the horizontal deviation of the eyes was to the left, the left eye was turned upwards, and the right downwards. To conclude, as Biehl does, from these observations (which are partially at variance with those of some experienced physiologists) that the stimulation experiment indicates the character of the normal working of the vestibular nerve appears hardly justifiable. We should rather assume that the vestibular root comprises so many different physiological entities, all in connexion with the preservation of static and dynamic equilibrium, that it will depend upon the details of the experiment as to what results will ensue from stimulation or injury of the root. Thus from my own experiments it would appear that a lesion of the proximal parts of the vestibular nuclei causes forced movements, the direction of which may be the reverse of that of movements caused by lesion of the caudal parts of the nuclei. It would, therefore, hardly be surprising if direct stimulation of the proximal and caudal fibres of the root produced oppositely directed conjugate deviations. Stimulation and section of the whole of the vestibular root gives evidence, I consider, of the function of the preponderant semicircular canal in that particular animal.

As regards the anatomical results in this group of animals we are considering, I must make particular mention of rabbit V, where the pars petrosa cerebelli, according to Bolk [26], or the so-called flocculus was extirpated, and a part of the vestibular nerve was injured, an associated lesion which occurs very rarely with this operation. Amongst a large number of experiments I consider this case the only one which can be utilized for the study of the intracerebral degeneration that occurs after a lesion of the vestibular root alone, since all other experiments in rabbits and cats showed, on careful microscopic examination, complications caused by associated lesions in adjoining regions. In this animal we could follow the degenerated vestibular nerve-sheaths into three cell groups, to the descending ramus of the vestibular nucleus, to Deiters' nucleus (both to its ventral distal division—nucleus triangularis—and to its dorsal large-celled division—Deiters' nucleus in the narrower sense), and to the region of Bechterew's nucleus and the nucleus tecti [112]. Meynert, Sala and Thomas also traced vestibular fibres directly into the roof nuclei.

In none of my numerous experiments with lesions of the vestibular nerve could I succeed in following the course of the root-fibres towards the area of the posterior longitudinal bundle and its lateral horns, or towards the pons or mid-brain, or descending directly into the spinal cord. In vain did I endeavour to convince myself, by means of the osmic acid method, of the existence of direct vestibular fibres which cross the raphe (Cajal and Wallenberg in birds, Deganello [46] in frogs, Lewandowsky in mammals). I should almost doubt that such fibres exist, although the silver method of Cajal strongly suggests them ; what may happen, with the osmic acid method, I think, is that in extensive injury of the elements of the vestibular nerve, a few fibres originating from Deiters' nucleus degenerate upwards, and thus simulate direct root-fibres. Further, I cannot agree with Lewy [91] that the structures in the posterior longitudinal bundle are more likely than those in other regions to contain fibres coloured by osmic acid. On the contrary, by carefully avoiding all compression of the brain, I have obtained ample proof that even extensive lesions of the cerebellum (including the nucleus dentatus) never cause the slightest degeneration in the posterior longitudinal bundle; in these cases I never observed the slightest sign of forced movements in the two planes (circus movement in the horizontal plane, and rolling movement in the vertical plane, vertical to the long axis of the animal) which are discussed in this paper.

As regards the striking difference in the physiological effects produced by the lesion in rabbit V, and those produced by all the other lesions of the vestibular root, I must observe again that the rolling movements in this case were never of a vehement character, and, as already stated, were directed to the side opposite to the lesion. Seeing that this sort of rolling movement never resulted in numerous other rabbits in which the flocculus alone was removed, together with the part of the nucleus dentatus enclosed in it [114], it must probably depend in this case upon the unusual lesion of the vestibular root that was present. In this case (rabbit V) it was especially the caudal part of the vestibular root and the ramus descendens that were degenerated, and the limited extent of the lesion is proved by the absence of degeneration in the tuberculum acusticum and the corpus trapezoides.

§ 2.—*Lesion of the Descending Ramus of the Vestibular Nucleus (Table I, Group* 7, p. *376*).

The next group to be considered contains the animals with lesion of the descending ramus of the vestibular nucleus; either a total destruction of the cell area as in cat No. 8 (fig. 9) or a partial lesion as in Nos. 18 and 35. The chief point in connexion with this lesion is that in these cases rolling movements to the healthy side, or at any rate an inclination thereto, were observed during the life of the animal. The intensity and the duration of these rolling movements and of the corresponding deviation and rotation of the eyeballs around their axes that accompanied them [107, 113] appear to be in direct proportion to the intensity of the lesion in this part of the vestibular complex, or to the completeness with which, as in some other experiments, this part

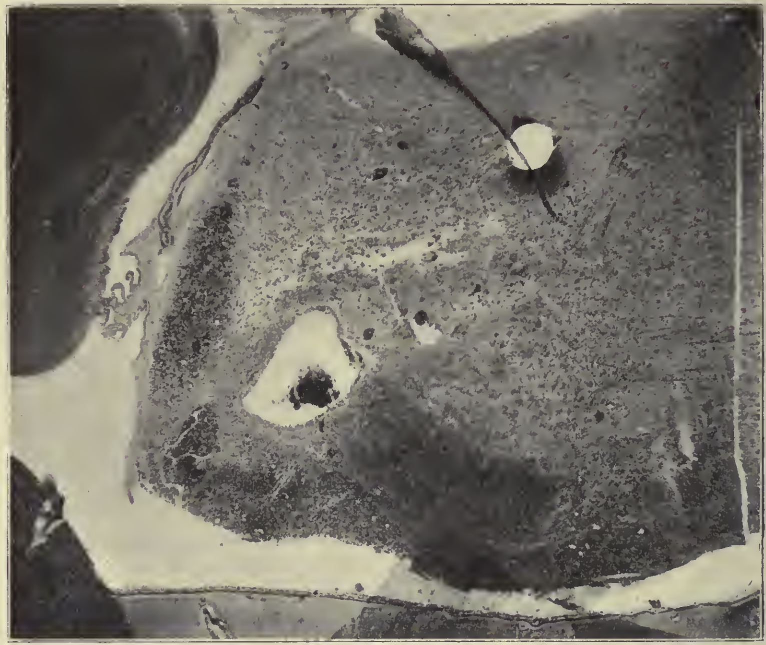


FIG. 9.—Lesion of the medulla oblongata of cat 8, softening with cystic degeneration, including the ramus descendens nuclei vestibularis.

of the complex is cut off from the raphe, and from the more proximally situated parts of the cerebrum.

In cat No. 8 we have to deal with a complete cystic degeneration of the entire region (fig. 9). In cats Nos. 18 and 35, the lesion is partial only and caused apparently by indirect temporary pressure; in the latter of these two animals rolling movement never actually ensued. In cat No. 146 it was the distal part of the ramus descendens only that was cut off from the raphe and the proximal parts of the brain; in cat No. 158 the sagittal lesion was immediately lateral to the left posterior longitudinal bundle and severed the entire vestibular region from the raphe (figs. 10*a* and 10*b*). This last animal fell for several days towards the side opposite the lesion.

I must admit that my material is inadequate to allow the conclusion to be drawn absolutely that this part of the vestibular system specially controls this function of rolling movements towards the non-severed side, or rather this negative function, because, according to Munk [106] rolling movements are to be considered as the result only of an inability to maintain the normal posture. However, I consider this conclusion is in accordance with the facts so far obtained by a physiological analysis of the Deiters' complex, and it is such a relatively rare occurrence that, after a lesion of the descending ramus, an animal remains alive long enough to admit of observations being made, that I consider these preliminary results worth noticing. I have to confess that all the lesions in this group involved accidentally the ramus descendens. Only once did I succeed in my attempts to produce a lesion of the descending branch and in this way to observe rolling movements towards the healthy side.

As regards the secondary degenerations which are due to a lesion of the ramus descendens, it is only in No. 158 that I have been able to obtain positive (?) data. In this animal an ascending degeneration is present in the mesial part of the lateral horn of the posterior longitudinal bundle (fig. 10*b*), but the situation and the extent of the sagittal lesion in this case are not such as to justify us in concluding that this ascending bundle actually originates in the ramus descendens of the vestibular nucleus; probably it is the one which was affected in the case discussed in § 5 of this chapter. This much is certain, however, that in cat No. 8, with a complete destruction, and in cat No. 18, with a slight lesion of the ramus descendens, there is strangely enough only the merest trace of ascending degeneration in the heterolateral posterior longitudinal bundle, and at the same time only exceedingly

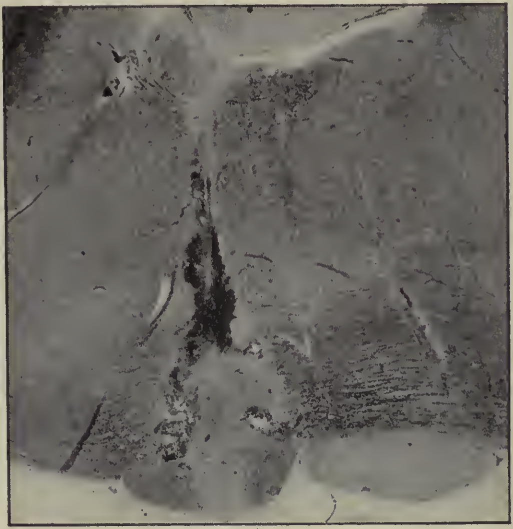


Fig. 10*a*.

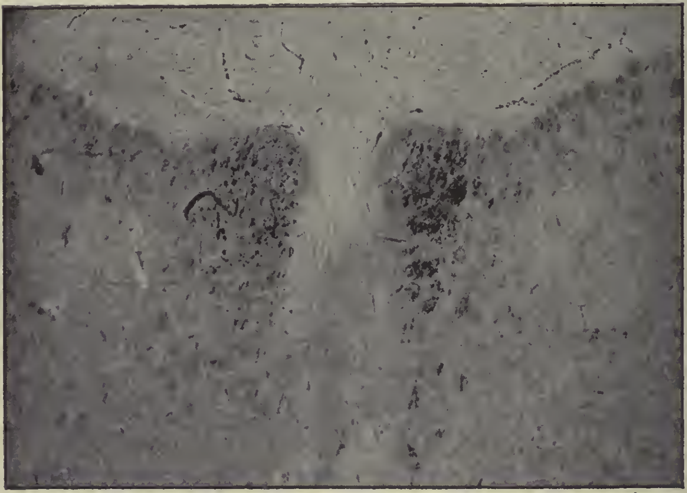


Fig. 10*b*.

FIGS. 10*a*, 10*b*.—Taken from cat 158.

FIG. 10*a*.—Sagittal lesion on the left side of the posterior longitudinal bundle, cutting off the vestibular region from the raphe.

FIG. 10*b*.—Ascending degeneration in the region of the nucleus tegmenti profundus. Note also degeneration of the tractus vestibulo-mesencephalicus cruciatus.

slight descending degeneration either on the side of the lesion or on the opposite side. As to No. 158 the degenerated fibres may be merely crossed ones.

In the literature I find certain facts which are in support of my views. This is the case in the discussion by Longet [94] on the rolling movements which occur after a lesion behind the fifth nerve. Luciani and Sergi [96] confess that they cannot explain why, after lesion of the lower posterior part of the cerebellum, rolling movements should appear which take an opposite direction to those seen after ablation of a hemisphere. Russell [138] observed the same movements after lesions of the restiform body.

As it is impossible for a lesion to be confined absolutely to the ramus descendens, the restiform body being usually involved, it might be suggested that the ascending olivo-cerebellar fibres took part in this phenomenon. If, however, it be considered certain that all the olivo-cerebellar fibres terminate in the cerebellar cortex, the fact that no lesion of the cerebellar cortex alone is associated with the demonstration of this phenomenon renders the supposition improbable.

§ 3.—*Lesion of Deiters' Nucleus* (*Table I*, *Group* 8, p. 376).

In two animals (Nos. 113 and 118) the lesion was limited to Deiters' nucleus on the right side (Group 8 of Table I). In both these animals, circus movement to the side of operation was observed. In Chapter I, §§ 1 and 3, I have discussed the crossed ascending degeneration of fibres, passing from this nucleus into the posterior longitudinal bundle, and in these two animals there was also a falling movement to the side of the lesion as well as a circus movement. In both animals ascending degeneration was found in the most lateral part of the lateral horn of the posterior longitudinal bundle, and could be followed in an upward direction as far as the region of the tegmentum. A few fibres, however, could be followed into the posterior commissure at its extreme caudal level (lateral fibres seen in fig. 3*b*, on right side).

In § 4 of this chapter, it is shown that a direct lesion of the lateral part of the posterior longitudinal bundle is followed by an ascending degeneration of the fasciculus vestibulo-tegmentalis lateralis, which is in all cases accompanied by rolling movements towards the side of the lesion.

After a careful examination of the cases and their anatomical lesions, one feels bound to admit that different parts of Deiters' nucleus control the circus movements to the operated side, and the rolling movements towards the side of the lesion. This is illustrated in cases Nos. 113 and 118. In the first case the circus movements lasted a whole week, while in the second they were present for one day only; in the first case the entire caudal triangular part of Deiters' nucleus was injured, and the ascending crossed vestibulo-mesencephalic bundle was far more extensively degenerated than in the second case. From the physiological analysis one may further deduce that the magno-cellular part of Deiters' nucleus, or what is termed Deiters' nucleus in the narrow sense, which controls the rolling to the side of the lesion, sends out more descending fibres towards the spinal cord on the side of the lesion, than the ventral part which controls the circus movements to the side of the lesion.

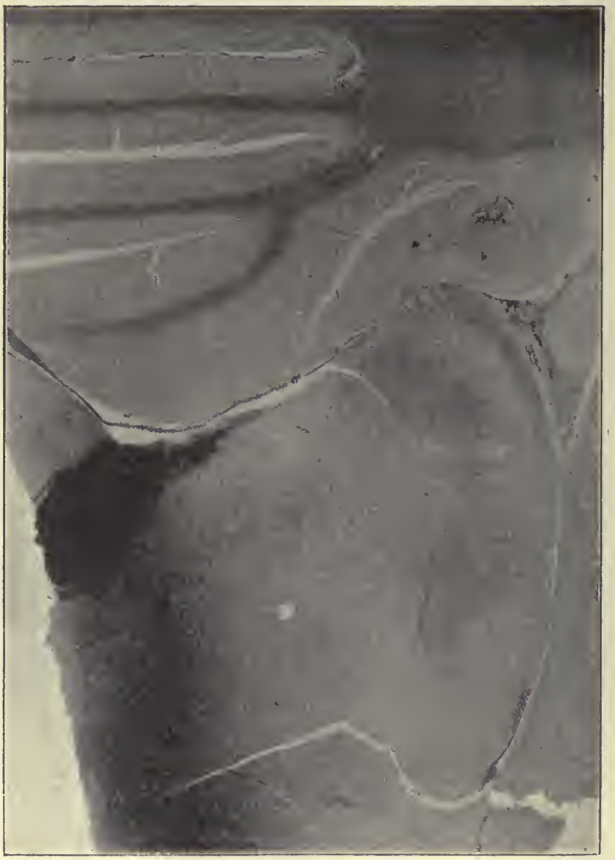


Fig. 11*a*.

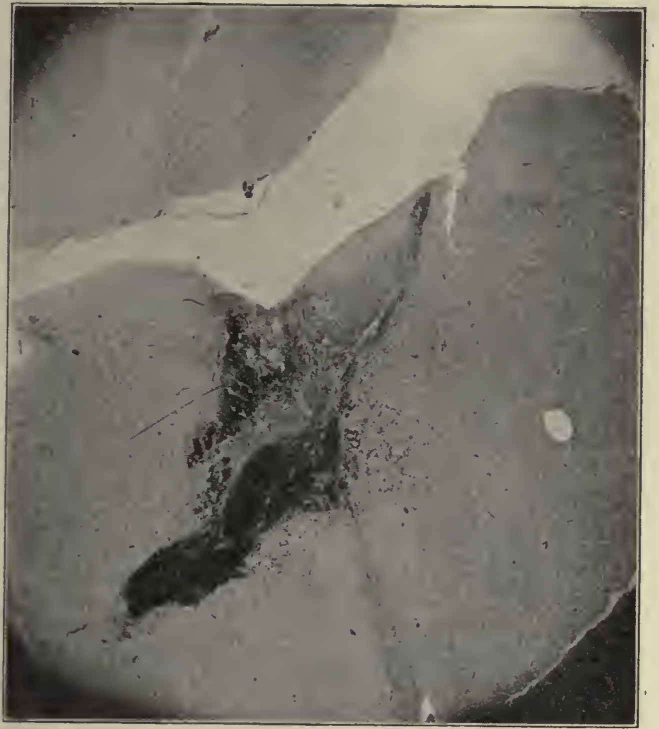


Fig. 11*b*.

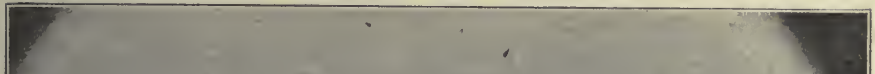


Fig. 11*c*.

Figs. 11*a*, 11*b*, 11*c*.—Cross-sections of cat 90.

Figs. 11*a* and 11*b*.—Lesion of the posterior longitudinal bundles in the pontine region. Note destruction of the lateral horn on the right side.

Fig. 11*c*.—Ascending degeneration of the lateral horn on right side.

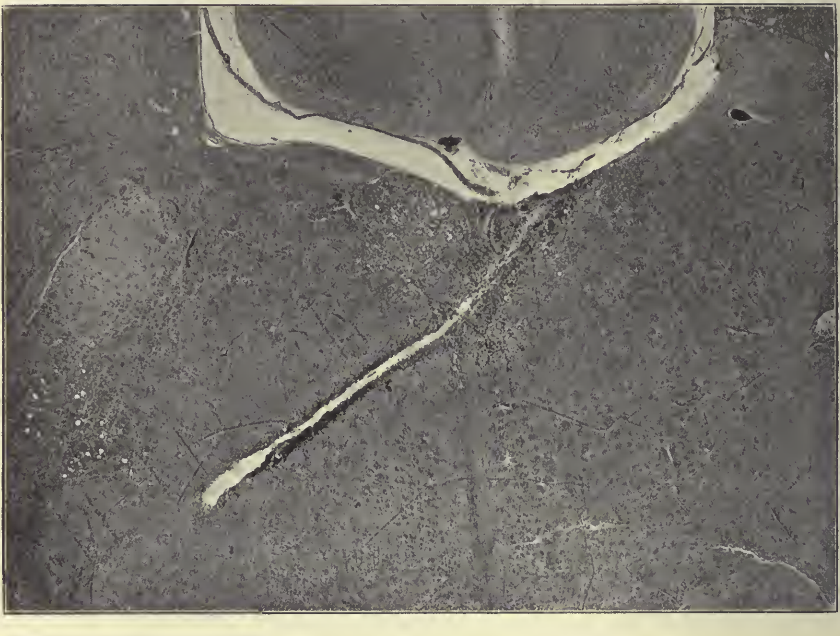


FIG. 12*a*.

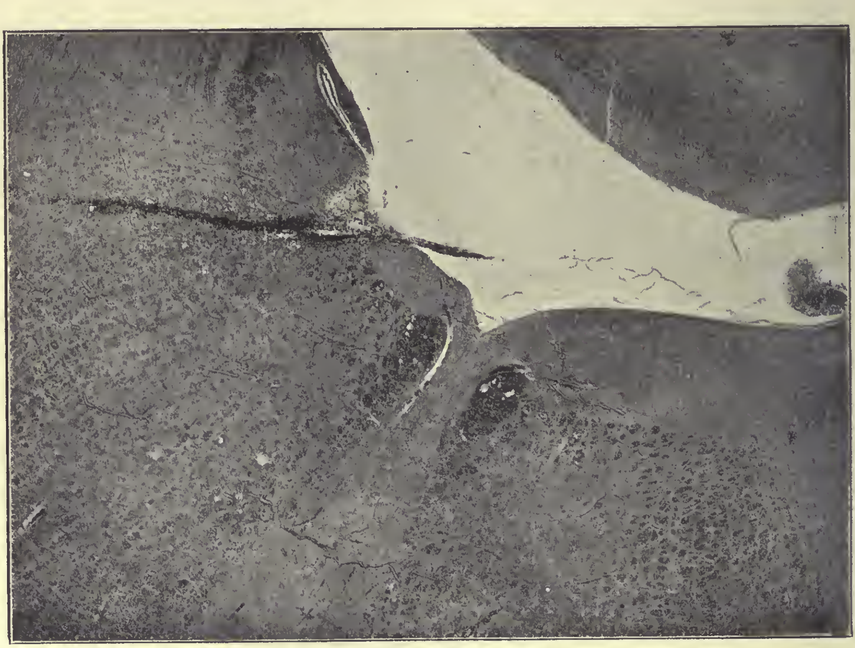


FIG. 12*b*.

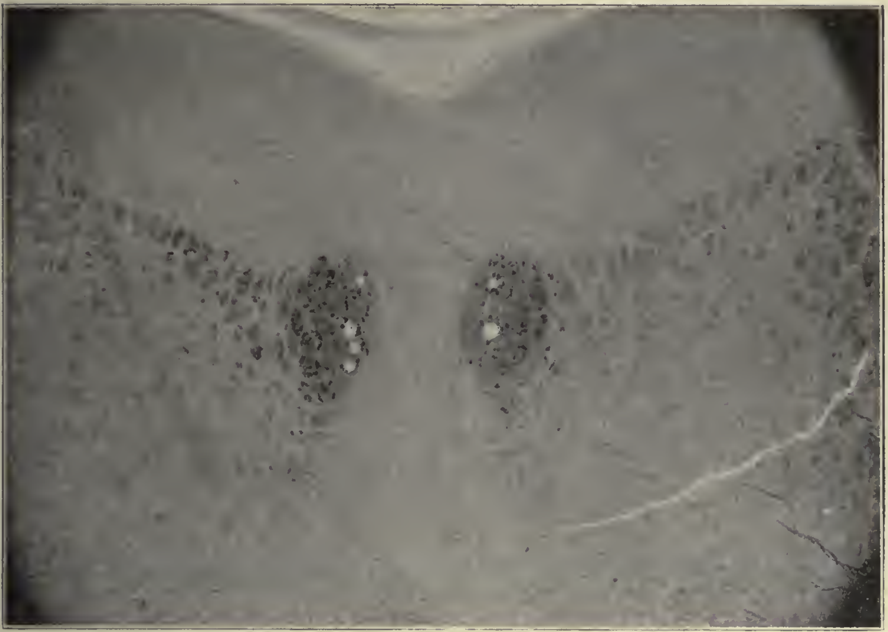


FIG. 12*c*.

FIGS. 12*a*, 12*b*, 12*c*.—Cross-sections of Cat 92.

Figs. 12*a* and 12*b*.—Lesion of the posterior longitudinal bundles in the pontine region. Note destruction of the lateral horn on the left side.

Fig. 12*c*.—Ascending degeneration of lateral horn on left side.

As has already been pointed out in Chapter I, § 3, it has not yet been possible to determine which part of the homolateral, and particularly of the heterolateral descending posterior longitudinal bundle fibres originate in the reticular cells (fasciculus reticulo-spinalis), and which from Deiters' nucleus.

§ 4.—*Lesion of the Lateral Horn of the Posterior Longitudinal Bundle* (*P.L.B.*) *or Fasciculus Deiters' Ascendens* (*F.D.A. of Lewandowsky and Winkler*) (*Table I, Group* 9, p. 376).

The following groups of experiments (Groups 9 and 10) concern the direct lesions of the lateral part of the posterior longitudinal bundle), which is acknowledged by Winkler [169], Lewandowsky [89], and van Gehuchten [63], to be an anatomical entity, and named by them the fasciculus Deiters' ascendens (F.D.A.), or faisceau triangulaire.

Special attention should be paid to experiments Nos. 90 and 92 (cf. the diagrams of the table, Group 2, and the figures 11*c* and 12*c*), because in those animals both the posterior longitudinal bundles were cut between the sixth and fourth nuclei. In No. 90 the *right* fasciculus Deiters' ascendens was also cut (figs. 11*a*, 11*b*), while in No. 92 the *left* fasciculus Deiters' ascendens was cut (figs. 12*a* and 12*c*).[1]

We here observe a remarkable parallelism between the physiological and anatomical data given in the table. In Case 90, where the right fasciculus Deiters' ascendens was severed, it showed degeneration upwards to the right, while the animal displayed a rolling movement to the right side. In Case 92 the left fasciculus Deiters' ascendens showed degeneration upwards to the left, while the animal also displayed a rolling movement to the left side.

In not a single case was there any trace of a lesion in either the vestibular root, Deiters' nucleus, or the ramus descendens of the eighth nucleus, which might be the cause of this phenomenon.

In Case 114 both the posterior longitudinal bundles were severed orally to the fourth nucleus, while the right fasciculus Deiters' ascendens was also cut. In this case it was only in epileptic fits induced by camphor monobromate that falling to the right side was observed.

In the next five experiments the extreme lateral part of the fasciculus Deiters' ascendens was either injured directly, or it was found degenerated in consequence of a lesion of Deiters' nucleus associated with extirpation of a cerebellar hemisphere.

In some cases, such as No. 150 (cf. also Quensel's case No. 1 [128]), only the extreme lateral fibres of the fasciculus Deiters' ascendens were affected on one side, yet the animal showed a decided tendency to fall to the same side. In such cases the ascending degeneration can only be followed for a short way, which evidently shows that these lateral fibres lose their sheaths immediately they enter the region of the posterior commissure.

It is not necessary to go further into detail concerning these experiments, seeing that the diagrams of the table (Group 9) furnish all the necessary data.

From a consideration of the data it seems probable that there is a vestibular ascending bundle (or one of several such bundles) in the lateral part of the fasciculus Deiters' ascendens, which controls the rolling movements to that side. This bundle may be termed the fasciculus vestibulo-tegmentalis lateralis.

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[1] As regards the circus movements to the right shown by Case 90, it should be remembered that in this animal hæmorrhage ensued into the posterior longitudinal bundle, which presumably caused an unequal lesion of the mesial parts of the posterior longitudinal bundles, causing circus movement.

From the results obtained after lesion of the principal division of Deiters' nucleus (Chapter III, § 3), it may be deduced that the medium or small cells of the dorsal division of Deiters' nucleus (that is Deiters' nucleus in the narrow sense) constitute the origin of this bundle. This conclusion is come to in consequence of the total degeneration of the giant cells seen after hemisection of the cervical cord (v. Monakow [104]).

In numerous other lesions made in the pontine region I have never observed any rolling movement when the vestibular nuclei and their ascending systems remained intact. I can further confirm for one experiment the observation of Spitzer and Karplus [150], that a longitudinal incision in the middle cerebellar peduncle is not associated with circus movements.

§ 5.—*Lesion of the Mesial Part of the Fasciculus Deiters' Ascendens* (*F.D.A.*). (*Table I, Group* 10, p. 376).

Among the numerous experiments in which lesions were made in the region oral to the Deiters' nucleus, there are certain cases which are in apparent conflict with the results discussed in the foregoing paragraph as regards the physiological phenomena, and also, I believe, as regards the anatomical data.

In none of these cases did the rolling movements actually appear. At most there was a tendency for the animal to roll or fall on to the non-operated side. In Case 91 there was found only a slight degeneration of the left vestibular root and of the right Deiters' nucleus which might possibly account for this phenomenon.[1]

In the other cases I can assign no cause for this tendency to fall towards the normal side.

In these three cases under consideration there is an ascending degeneration predominating in the mesial part of the fasciculus Deiters' ascendens which appears to me to afford good ground for supposing that there is an ascending vestibular connexion with this part of the fasciculus Deiters' ascendens, which controls the rolling movement to the healthy side (fig. 13).

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[1] Although I have considered it necessary for the physiological analysis of the posterior longitudinal bundle to exclude all the cases in which collateral injury of the vestibular roots and Deiters' nucleus occurred, it yet appears highly improbable in Case 91 that the slight lesion of these parts was the cause of the protracted inclination to fall to the non-operated side. If we accept this, the case would bear out what is maintained in this paragraph. In Case 68 the objection is justified that the same injury which caused degeneration of the descending fifth root and of the restiform body on the right side, may have involved the descending eighth root on the same side.

In these cases there is a moderate descending degeneration in the spinal posterior longitudinal bundle of the same side, down to the dorsal region.

There are, however, too few cases to allow of any positive conclusions being formed as to the existence of such a bundle.

Should further investigation, however, confirm this supposition, the bundle might appropriately be named the fasciculus vestibulo-tegmentalis medialis. (Cf. the ascending degeneration in the posterior longitudinal bundle on the left side in Case 91, fig. 13, and Case 158, fig. 10*b*, respectively.)

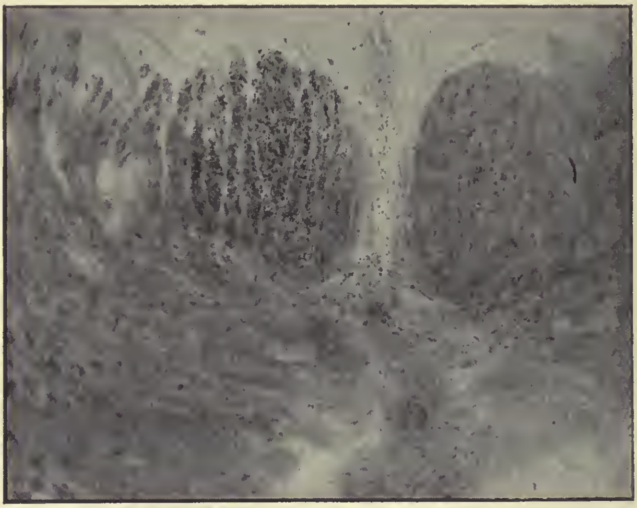

FIG. 13.—Taken from cat 91 (Table I, Group 1, p. 376). Ascending degeneration after section of the posterior longitudinal bundle on left side. Note degeneration of fibres on the left side of the area in fig. 3*b*.

If the experiments and anatomical data contained in Chapter III, § 2, be considered, it would seem possible that the cases dealt with in this section demonstrate a secondary ascending connexion of the descending ramus of the vestibular nucleus. As evidence in support of this view are the three cases (VIII, Nos. 18 and 35) where, after lesion of this part of Deiters' nucleus rolling movements to the non-operated side followed. As, however, it was impossible in these three cases to determine positively that there was an ascending degeneration in the posterior longitudinal bundle after lesion of the ramus descendens, with the Marchi method, one is not justified in drawing any further conclusions. Unless we can assume that the axons which ascend from that part of the vestibular nucleus form a synapse with an adjoining group of cells—e.g., in the nucleus triangularis or nucleus raphe—we are unable to explain the exceptional behaviour of the ramus descendens as compared with all other primary centres of the vestibular nerve. In the light of the physiological facts brought forward in §§ 4 and 5 of this chapter, it is interesting that according to Cajal (vol. ii, p. 267) the collaterals from the posterior longitudinal bundle to the fourth nucleus take their origin, without exception, from the *lateral* parts of the posterior longitudinal bundle.

CHAPTER IV.—A CENTRIFUGAL BUNDLE WHICH CONTROLS THE ROLLING MOVEMENTS TO THE NON-OPERATED SIDE.

In Chapter II the material of this investigation was considered with reference to its bearing on the supposition of several authors, anatomists, physiologists, and clinicians, that not only the centripetal bundles which control the equilibrium of motion in the horizontal plane form an important part in the posterior longitudinal bundle, but that the tracts which control that function in a centrifugal sense also find a place in this structure. Table II, p. 378, certainly contributes fresh evidence in favour of this supposition. In those animals where a lesion of the ventral part of the mid-brain is associated with circus movements towards the side of the lesion the probability is certainly furnished of the existence of a descending bundle which originates in the region of the posterior commissure. The experiments not only confirm the law of Schiff and Probst ("after hemisection of the posterior part of the optic thalamus circus-movements follow to the side of the lesion"), but they furnish experimental data which tend to prove that in such cases the lesion of a certain group of cells and the consequent degeneration in the extreme mesial part of the posterior longitudinal bundle are responsible for this form of forced movements. The conclusion is therefore arrived at that the maintenance of the equilibrium in the *horizontal* plane is assured by a double system of ascending connexions situated on either side of the mesial line, and also by a descending tract between the posterior commissure and the region of the vestibular nuclei. This system of tracts shows distinct connexions with the nuclei of the ocular nerves, which are quite sufficient to explain the conjugate deviation of the eyes in the horizontal plane which regularly accompanies the circus movements.[1]

Owing to the descending connexions with the medulla oblongata, the concomitant action of the neck, trunk, and extremities may be regarded as assured. By means of this double system the compensatory movements of the head and eyes are accomplished after unilateral lesion of the tracts, either ascending or descending, which are associated with circus movement and conjugate deviation in the *horizontal* plane of the eyes.

In conclusion, the experiments made in connexion with this investigation are examined as to their bearing on the question of the arrangements for rotatory movement, or locomotion in a plane vertical to the long axis of the animal. Is there an arrangement of tracts similar to that involved in the forced movements already discussed?

Physiologists, anatomists, and clinicians have shown less interest in this problem than in that dealing with the circus movement and conjugate deviation in the horizontal plane. This is partly due to the fact that this particular form of conjugated deviation (Hertwig-Magendie squint) is only rarely met with in pathological conditions, and also because the rolling and allied phenomena seen in physiological experiments are but very imperfectly understood.

Vulpian [159], Schwahn [145], Russell [138], and recently Biehl [21], have proved that as a forced movement or as a forced position it appears especially after lesion of the restiform bodies.[1] Hogyes [70], and Kubo [84] have noted this form of squint as a reflex phenomenon brought on by certain passive rotations of the head. Hunnius [75], MacGregor [97], and Stewart and Holmes [71], have found it in cases of cerebellar and pontine tumours. Friedberg [60] and Meynert also observed true rolling movements. In diseases of sheep it appears to have distinct diagnostic value [152]. An extensive literature such as there is on the subject of conjugate deviation in the horizontal plane is quite lacking.

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[1] The conjugate deviation of the eyes and neck is directed, as a rule, towards the same side as the circus movement, but Grasset [66] maintains there are exceptions to this rule. This author observed a case where there was conjugate deviation of the eyes to one side and lateral deviation of head to the other side. He ascribed this occurrence to an uncommon combination of lesion in different tracts. A case which illustrates this better is that reported by Kooyker [83] where a hæmorrhage had occurred in the upper part of the internal capsule on the right side. As a result, there was conjugate deviation of eyes to the right and deviation of the head to the left side so long as the symptoms of irritation were present. It must be admitted that besides the destruction of some tracts others were probably subjected to irritative lesions. (Cf. Chapter VII.)

Another very common combination in all classes of vertebrates (cf. 211 and 217, p. 107) is circus movement to one side and rolling movement to the other. This is, of course, easily explained by the peculiar arrangement of the ascending vestibulo-mesencephalic and the descending mesencephalic tracts (fig. 14). This rule also has its exceptions which can be accounted for by an unusual combination of lesion. Thus in No. 108 (cf. Group 11 of the table) the interstitio-spinal tract on one side and the commissuro-medullary tract on the other side are degenerated, while the animal shows a rolling movement to the left side, combined with a circus movement to the same side. In sharks and frogs I found this association of circus movements to one and rolling movements to the other side a very common combination; also in octopods after extirpation of one otolith [110]. It is of interest to note that equally in crustaceans unilateral lesions of the central plexus is associated with circus movement to the intact side and rolling movement to the other side [47].

The rare occurrence of the skew deviation in the higher organized animals with a combined visual field is explained by Clarke, working in Horsley's laboratory, as a vestigial trace of a former phylogenetic condition where this form of squint was a useful reflex mechanism associated with monocular vision! Where so little is known about the phenomenon and the centripetal tracts controlling it in experiment or in disease, it is not surprising that, so far as I am aware at least, the problem as to whether there exists a tract or centre, the descending degeneration or lesion of which is associated with a rolling movement round the axis of the body and other minor allied symptoms, has not arisen. This problem is embodied in the question as to whether in the present investigation there is any experimental evidence of a descending tract originating from a centre in the region of the posterior commissure which when degenerated is associated with rolling movements and allied phenomena.

The Table II and Chapter II afford information about the tracts which were found to be degenerated in or about the posterior longitudinal bundle after lesion in the region of the posterior commissure. They are: (1) the fine fibred commissuro-medullary bundle; (2) the thick fibred interstitio-spinal tract;[2] (3) the bundle lateral to the posterior longitudinal bundle described by Probst, Economo and Karplus, and van Valkenburg [158]. From the physiological analysis of the cases where circus movement was found, it seemed highly probable that the commissuro-medullary bundle is the centrifugal tract controlling this movement.

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[1] The author disposes of several extensive degenerations of this body in animals that performed no forced movements.

[2] The interstitial nucleus was recognized to be an anatomical entity in fishes by Fritsch and Mayser before Cajal (1896) described it; the nucleus commissuræ posterioris, lying caudally to the radiation of the posterior commissure, by Darkschewitch. The commissuro-medullary tract was not, so far as I am aware, described until my paper appeared in 1912 [108]. In this paper I described the origin and termination of this tract, and of the interstitio-spinal tract of Boyce and Cajal (1895). The same subject was dealt with in a second paper which was published in 1913 [109]. The existence of the commissuro-medullary tract was, however, strongly indicated by the interesting data collected by Kohnstamm and Quensel [80] on axonal reactions in the commissural region after a lesion of more caudal parts.

In this connexion (rolling movements) we have to consider the second and third of the descending bundles especially. If the cases where the rolling movements or some of the allied minor phenomena were maintained for a longer period be picked out, then the Cases 107 and 108, the case of Probst and that of cat No. 3, recorded by Economo and Karplus, stand apart. From the consideration of these cases it was concluded that the interstitio-spinal tract was degenerated on the side of the lesion in the post-thalamic region. Further, in these animals the rolling movements or allied phenomena were always towards the normal side. The question now arises: Is this a simple coincidence or is the rotation dependent on the degeneration of the centrifugal limb of a reflex mechanism for the equilibrium in the plane vertical to the long axis of the animal?

As yet I do not consider that sufficient evidence has been collected to allow of a definite decision being come to on this point, but the question is one well worthy of further investigation.

Only in very localized lesions in the region of the posterior commissure was it possible to localize the probable origin of the interstitio-spinal tract, as the Marchi method in most cases is worthless for recognizing definite cell groups.

Case 108 (fig. 7) afforded evidence for determining the lateral boundary of the origin of this tract, while Case 23 afforded evidence for the dorsal boundary. From such evidence the identity of this nucleus and tract with that described by Cajal is established, while they are definitely differentiated from the nucleus of the posterior commissure and its commissuro-medullary bundle.

The tract lateral to the posterior longitudinal bundle was first described by Probst [124, vol. xxiii, p. 54], and later by Economo and Karplus [78], and Besta [17]. It consists of a bundle of widespread delicate fibres which originate in the prærubral region, and, as shown in Case 108 (not in the figure), appear lateral to the nucleus interstitialis. It does not enter into relation with the third nucleus but descends on the same side latero-ventrally to the posterior longitudinal bundle, terminating in the ganglion tegmenti profundum (Gudden) immediately caudal to the fourth nucleus.

As already stated, I am not prepared either to deny or affirm that this tract has anything to do with the functions discussed in this paper.

I would, however, point out that it is exceedingly improbable that this tract corresponds with the descending tract of Collier and Buzzard [42], since in my preparations none of its fibres descend lower than the pontine region.

A study of the various lesions of the posterior commissure described by the above-mentioned authors and myself, leads to the conclusion that these fibres do not cross the commissure or the raphe. From the direction of the fibres it would seem that they originated in the nucleus intra-commissuralis of the same side, which lies in the middle of the commissure, antero-posteriorly. This nucleus, according to Kohnstamm [80], does not degenerate after hemisection of the cord, but after lesion of the brain-stem. Economo and Karplus [78], however, advance the theory that this tract originates in the corpus mammillare (p. 395, cat No. 3), while also the observations of Probst, Lewandowsky, Flatschek and van Valkenburg [158] seem to lend confirmation to the view that it is part of the tractus mammillo-tegmentalis.

On the whole the results of the present investigation tend to show that a lesion of the nucleus interstitialis (Cajal) is followed by a rolling movement towards the opposite side from the lesion. This direction of the movement is in agreement with the results obtained by v. Bechterew [10] in his experiments on the infundibular region in dogs.

In these cases the fasciculus interstitio-spinalis was found degenerated with such regularity that it seems highly probable that it contains the centrifugal limb of the superimposed vestibular reflex arc dealing with this function. Knoll [79] and Topolanski [155] by electrical stimulation of the region of the posterior commissure caused rolling movements towards the side of the irritation, i.e., opposite to the direction observed in my cases of direct lesion[1].

In this connexion it may be recalled that hemisection of the base of the mid-brain of the frog and fishes causes, according to Steiner, circus movements towards the non-sectioned side; this again is in accordance with our results with section of the posterior longitudinal bundle caudal to the nuclei of the posterior commissure. According to my own experiments on frogs and sharks the accordance between the experiments in lower and higher animals in this structure goes still further, in that also the lower animals, in performing this circus

[1] Pathological observations regarding this matter seem to be wanting. The only case, so far as I know, which was examined with the Marchi method was Case 4, recorded by Roussy [135], where the left eye is described as turned downwards, while the fasciculus interstitio-spinalis was degenerated.

movement, show a tendency to roll to the side of the lesion (cf. Flourens and Baudelot). A fundamental difference in these groups of animals lies however in the fact that in the lower ones no lesion oral to the commissura posterior brings about forced movements, whereas in the higher animals they do, the direction of these movements being inverse to that caused by a lesion of the posterior longitudinal bundle. Physiologically speaking, we have probably to deal here with a very old phylogenetic arrangement. At least it is interesting to note that Wallenberg [164, p. 393] came to the conclusion, on purely anatomical grounds, that the ventro-median part of the thalamencephalon of vertebrates subserves octavo-lateral functions, and is phylogenetically of far older date than the dorso-lateral part, which represents a recent acquisition and is associated with somatic sensory impulses.

The literature on the effects of the prosencephalon on conjugate deviation in the lower animals is very scanty and unsatisfactory. Boyce and Warrington [29] observed that in birds stimulation of the lateral ventral part of the fore-brain, or the origin of the strio-mesencephalic tract, is associated with conjugate deviation of the head and eyes to the other side. In fish, amphibians, and reptiles, both the free movement of the head and neck in the horizontal plane and the cerebral centre for this movement are probably too poorly developed to allow of the demonstration of conjugate deviation by electrical stimulation of the striate connexion of the posterior commissural nucleus. It has been shown above that in these animals, as in birds, the removal of one cerebral hemisphere does not produce the circus movements or conjugate deviation towards the side of the lesion seen in all the higher vertebrates (cf. Chapter VI).

CHAPTER V.—CONCLUSIONS AND DISCUSSION OF RESULTS.

§ 1.—*Plan adopted.*

The main object of this paper is to attempt to analyse the complicated vestibular system with its ascending and descending connexions by physiological and anatomical methods. Since it was demonstrated in a former investigation that a lesion of the posterior longitudinal bundle is primarily associated with two forced movements, it seemed possible that a study of these movements might help to elucidate a number of fundamental points, about the structure and function of Deiters' region and the posterior longitudinal bundle formation, where a purely anatomical analysis fails.[1] Thus Flechsig, v. Bechterew, Ziehen, and particularly Hösel [72] have drawn attention to the fact that some strands in the medulla and the posterior longitudinal bundle are the first to become myelinated. The presence of the posterior longitudinal bundle as a separate tract even in the lowest vertebrates, including the eyeless mammals, is but imperfectly understood. Further, it has long been known [116] that in embryonic rays, as soon as locomotion is possible, a fine puncture involving the posterior longitudinal bundle region causes vehement rolling movements so long as the umbilical cord permits.

These facts led us to adopt the phenomena observed after a localized lesion of the posterior longitudinal bundle formation as a starting point for such an analysis.

§ 2.—*Forced Movements and Semicircular Canals.*

In this analysis the vestibular nuclei must be considered as a system of cell masses, each one of which controls the condition of equilibrium in one of two different planes,[2] and is provided with separate ascending and descending connexions.

Flourens [57]; Spamer and particularly Breuer [31] and Kubo [84] have proved that irritation of any semicircular canal elicits movements in the plane coinciding with the canal experimented upon. Breuer and Kubo lay stress upon the fact that movement of the labyrinthine fluid towards the ampulla causes reflexly a conjugated movement of the eyeballs, in the direction opposite to that caused by movement of the fluid from the ampulla. Ewald [52] equally insists that each labyrinth rotates the head and eyes to either side. Each canal therefore should have a double representation in Deiters' complex. Hence in the schematic representation of the results of this investigation (fig. 14), a close functional relation is anticipated between the horizontal canal and Deiters' nucleus (triangular part), together with Bechterew's nucleus, and also between the anterior vertical canal and the descending branch of the nucleus vestibularis, together with the dorsal part of Deiters' nucleus. Should this relationship prove to be anatomically correct it does not of course indicate that the two forced movements, conjugated deviation and reflex nystagmus, coincide with the planes of the canals. It is almost certain that the anatomical arrangement of the skull and the customary mode of progression of the animal will also play a part. The latter factor will undoubtedly influence all reflex phenomena dependent on the vestibular system [32]. It may also be responsible for the prevalence of rolling movements after labyrinthine lesions in most vertebrates[1] for, according to Breuer [31], the mobility of those animals is most dependent on equilibration, in the plane vertical to their long. axis. Biach and Bauer [19] came to a similar conclusion, a result of their own experiments and those of Marburg and Bing on the ascending spino-cerebellar tract. In my schematic diagram (fig. 14) no reference is made to the otoliths which are probably, as Breuer [31], Kreidl and Kubo [84] believe, connected with the perception of linear movement, while the semicircular canals are associated with the perception of angular movement. Both organs are evidently closely associated in their action, and there is no doubt that hardly any movement of the head is associated with the stimulation of one semicircular canal only (Ewald [51]).

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[1] Although I personally prefer the Marchi method (Busch's modification) to any other, even to the combination of the Marchi and Nissl methods, which is increasing in popularity, yet I consider it inadequate to decide such questions as to whether the vestibular fibres terminate in Deiters' nucleus proper or not. In this region one is particularly liable to fall a victim to false conclusions, since any lesion of the posterior brain cavity, even the removal of the bone, may bring about slight degenerations in the cell masses. Here therefore is an opening for anatomo-physiological research, based upon a large number of experiments.

[2] In this communication the cell masses and ascending connexions which control forced movements in the third plane, that is the plane coinciding with the long axis of the body vertical to the horizontal plane and in which tumbling and staggering occur, are not discussed.

§ 3.—*Character and Mechanism of the Forced Movements, in Lower and Higher Animals.*

Although in the anatomical and physiological analysis of the posterior longitudinal bundle formation dealt with in this paper, parallels have more than once been drawn between the two forms of forced movements, it must be borne in mind that, from a physiological standpoint, the character of these movements, circus and rolling, is very different. The rolling movements when present and well developed are mostly characterized by their vehement nature, while the circus movements are quieter and more deliberate. Where both are present in a medullary lesion the rolling movements are nearly always the more conspicuous, in fact it is only after the rolling movements have been partly compensated for that the tendency to go to one side manifests itself; if both are present in thalamic and quadrigeminal lesions, the circus movements are far more pronounced.

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[1] An exception to this rule is found in turtles, where the shape of the carapace prevents any falling to the side. In these animals even lesions in the region of Deiters' nucleus do not apparently cause true rolling movements (Fano, Bickel [20]).

Usually, owing to the peculiar arrangement of the ascending and descending tracts in the posterior longitudinal bundle formation, subserving these functions, circus movement to one side is accompanied by rolling movements to the other side. This rule has in a large number of experiments its exceptions, owing to peculiar situation of the lesion. On this ground, as on many others, Brown-Séquard's and Prévost's doctrine on the identity of the two types of forced movements can no longer be maintained. This theory has until very recently found supporters amongst physiologists.

In a physiological sense, there are even more points of difference between the two forms of forced movement. Goltz has shown that after bilateral section of the cerebrospinal stem in the frog, the hind part of the brain which is still in connexion with the vestibular apparatus is sufficient to maintain equilibrium in the vertical plane, vertical to the long axis. If the animal be laid on its side it returns to the normal position, executing a rolling movement. From this the conclusion seems inevitable that for the maintenance of the equilibrium in the plane vertical to the long axis of the animal the peripheral reflex arc in the frog (anterior vertical canal—Deiters' complex —descending tracts into the spinal cord) is endowed with a certain amount of autonomy. It has not yet been proved that the lower vertebrates have like the higher a mesencephalic reflex arc in the posterior longitudinal bundle formation, which, with the medullary reflex arc, dominates the compensatory movements in the vertical and horizontal planes, but it is possible that such an arc does exist. It is noteworthy that in the lower vertebrates the direction of the forced movements does not change when the lesion extends to the region of the posterior commissure.

As to the higher animals, attention may be here drawn to the fact that both the peripheral reflex centres (for both types of forced movements) are provided with spinal axons, but far more important in one case than in the other. It may be recalled that the axons from Deiters' nucleus, as well as those from the nucleus interstitialis, descend into the sacral region, while from the Bechterew nucleus and from the nucleus commissuræ posterioris, they rarely reach beyond the cervical region.[1] If these physiological and anatomical differences be kept in view, and also the opinion urged by Breuer that the equilibrium in the plane vertical to the long axis of the animal is extremely delicate, more especially in quadruped vertebrates, and therefore in need of constant adjustment, it is evident that the different characteristics of the forced movements after cerebral lesion appear in a new light. The fact that distinct rolling movements are never observed after cortical lesions of the cerebral hemisphere supports the view taken by Hughlings Jackson, that the cerebellum acts as a reinforcing organ for the function of gait and station represented in the mesencephalon, independently from the pyramidal tracts. Prus [127], in his experiments, demonstrated that the co-ordinated running about movements induced by stimulation of the lenticular nucleus are not interfered with by section of the pyramidal tracts.

Further the experiments of Mingazzini [101], Probst [123], Karplus and myself, all furnish evidence in favour of the view that the pyramidal tracts have little influence on locomotion in the quadruped.

The readjustment of the normal position in a plane vertical to the long axis of the animal requires an instantaneous activity of its reflex arcs. I hold that the tonic influence of the cerebellum [Luciani 95] by virtue of its relationship with the vestibular and kinæsthetic impulses (Jelgersma, Lewandowsky, and Lusanna's doctrine) is an indispensable factor. Its absence in cerebellar disease has lately been clearly demonstrated by Babinski's adiadokokinesis. Thomas [154] and Cajal rightly insist that the reflex arrangement, which brings about instantaneously the compensatory movements that ensure the maintenance of the equilibrium during any voluntary movement, largely depends on vestibulo-cerebellar connexions and the cerebellum. Whether, as Bolk [26] and van Rynberk [139] think, this function has a definite localization in the cerebellar lobes is uncertain, but it seems rather probable, since the afferent tracts are not spread diffusely over the entire organ. Magnus and de Kleyn's labyrinthine reflexes depend probably exclusively on our peripheral reflex arcs, which, by virtue of the transverse section in the mid-brain, have acquired a certain amount of autonomy.

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[1] It is also very interesting to note the fact recorded in the paper of Magnus and de Kleyn [98] that rotation of the head influences reflexly the innervation of the extremities and consequently their position. Lateral deviation in the same mammals has, on the other hand, no apparent influence.

§ 4.—*Forced Movements after Lesion of Deiters' Complex and Ascending Connexions.*

As the result of experiments on different parts of Deiters' complex, the following conclusions have been come to. As regards locomotion in the horizontal plane:—

(1) Circus movement *towards the affected side* is seen after lesion of the triangular part of Deiters' nucleus and after destruction of its *crossed* vestibulo-mesencephalic tract, originating in this nucleus.

(2) The circus movement, or rather conjugate deviation, is *towards the non-affected* side after lesion of Bechterew's nucleus and the *homolateral* vestibulo-mesencephalic bundle which originates in this nucleus.

It is therefore physiologically demonstrated that there is a functional difference between these nuclei and also between their ascending and descending connexions.

As regards the locomotion in the vertical plane, vertical to the long axis of the body, experiments on the ramus descendens of the vestibular nucleus and on the magno-cellular dorsal portion of Deiters' nucleus, or Deiters' nucleus proper, lead to forced movements in this plane.

(3) Rolling movements *towards the affected side* are seen after lesions of Deiters' nucleus proper, and the lateral horn of the posterior longitudinal bundle *of the same side* or tractus vestibulo-tegmentalis lateralis, that originates in that nucleus.

(4) Rolling movements *towards the non-affected side* appear to occur after lesion of the descending branch of the vestibular nucleus, and also, it appears, in some cases after a local lesion in the mesial portion of the lateral horn of the posterior longitudinal bundle on the same side. This bundle, if proven to exist, may probably be termed the tractus vestibulo-tegmentalis medialis.

From these anatomical and physiological facts we are inclined to infer that the horizontal and anterior vertical canals of each side are doubly represented in the vestibular complex of that side.

§ 5.—*Localization of Tracts in the Posterior Longitudinal Bundle Formation.*

In fig. 14 the relative positions of the six tracts which lie in the posterior longitudinal bundle formation and control the forced

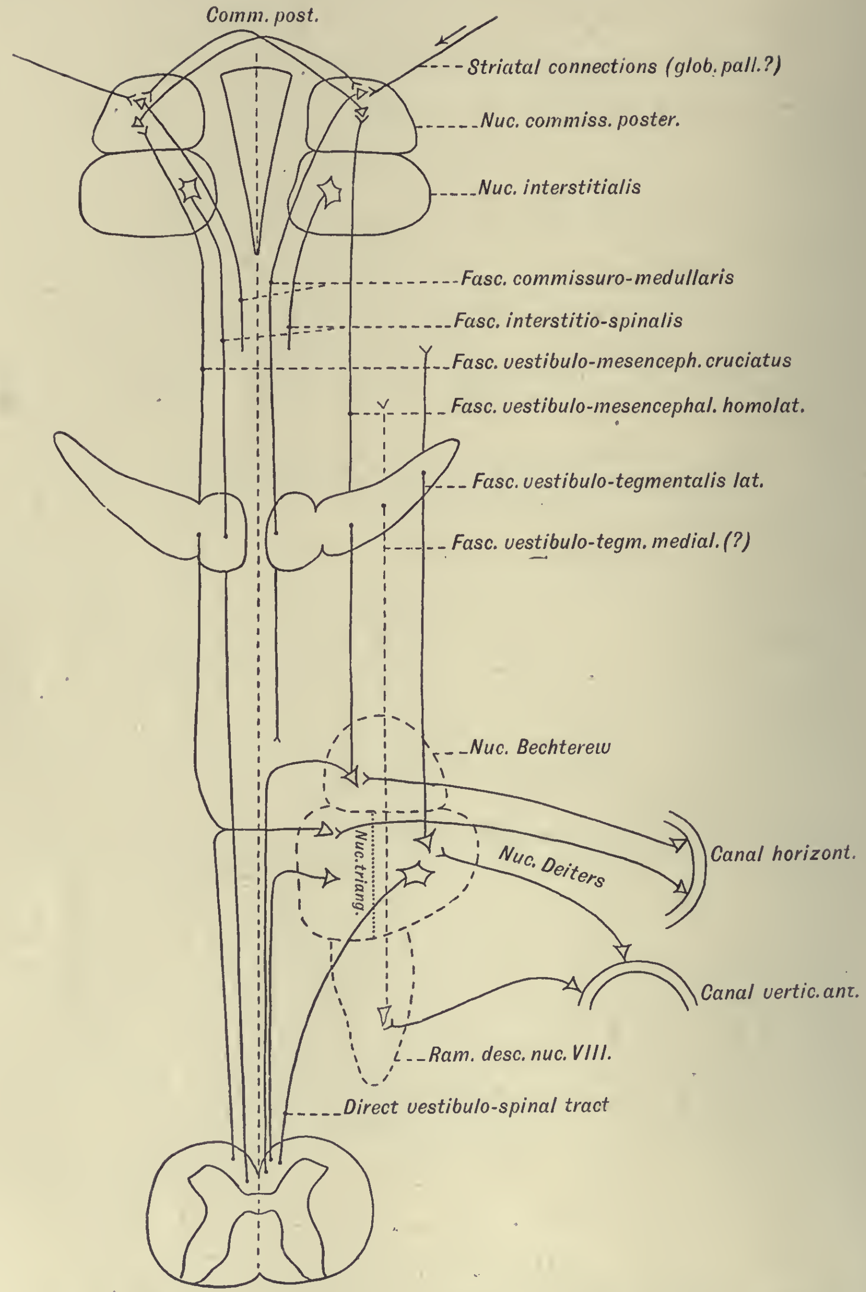
Comm. post.
Striatal connections (glob. pall.?)
Nuc. commiss. poster.
Nuc. interstitialis
Fasc. commissuro-medullaris
Fasc. interstitio-spinalis
Fasc. vestibulo-mesenceph. cruciatus
Fasc. vestibulo-mesencephal. homolat.
Fasc. vestibulo-tegmentalis lat.
Fasc. vestibulo-tegm. medial. (?)
Nuc. Bechterew
Nuc. triang.
Nuc. Deiters
Canal horizont.
Canal vertic. ant.
Ram. desc. nuc. VIII.
Direct vestibulo-spinal tract

FIG. 14.—Schematic representation of tracts and centres, discussed in this paper. According to Bernheimer, the hemispheral connections with the nucleus commissuræ posterioris should be exclusively crossed ones.

movements in the two planes[1] are demonstrated. In the innermost segment lies the finely granular tractus commissuro-medullaris and the coarsely granular tractus interstitio-spinalis. The rest of the posterior longitudinal bundle formation consists exclusively of centripetal tracts which ascend from Deiters' complex. The ascending fibres lying in the posterior longitudinal bundle are arranged in the following manner from within out: First is the crossed tract which ascends from the nucleus triangularis; next is the homolateral vestibulo-mesencephalic tract which ascends from Bechterew's nucleus. The tractus vestibulo-tegmentalis lateralis, which is an ascending tract from Deiters' nucleus proper, lies in the most lateral part of the posterior longitudinal bundle, while a tractus vestibulo-tegmentalis medialis, possibly originating from the ramus descendens, is supposed to lie mesial to it.

Generally speaking, therefore, the centrifugal fibres lie in the cat at the inner margin of the posterior longitudinal bundle. Next in order are the crossed fibres, and then the homolateral fibres (this agrees with Wallenberg's findings in birds). The bulk of the fibres of the posterior longitudinal bundle formation, oral to the vestibular complex, is therefore composed of tracts carrying centripetal impulses associated with the equilibrium of motion in the two principal planes. Since the centrifugal tracts which participate in the posterior longitudinal bundle formation appear to be equally associated with locomotion in these planes, the supposition advanced by Cajal, Spitzer [149], Kohnstamm [81], Hogyes, Marina [100], and others, that the posterior longitudinal bundle formation in the brain-stem and medulla is primarily associated with reflex locomotion in these planes, together with allied compensatory movements necessary for equilibration, seems justifiable.

The only nerves which besides the vestibular have an important reflex action on this system are the optic and acoustic (less so the olfactory) nerves; all three are situated orally to the vestibular complex. It is not surprising, therefore, that, as the researches of Wallenberg, Fraser [59], Probst, and Kohnstamm have shown, there are probably no centripetal fibres below the vestibular complex at all.

When the results of a series of lesions made in the posterior longitudinal bundle formation from the vestibular complex to the posterior commissure are considered from the physiological standpoint, two facts become evident. First, the forced movements caused by ascending degeneration of the vestibulo-mesencephalic and vestibulo-tegmental tracts are of correspondingly shorter duration the nearer the lesion is to the posterior commissure. As a matter of fact, it has also been noted by v. Bechterew [12] and Lewandowsky [89] that forced movements after mesencephalic lesions are of a less pronounced character than those seen after lesion of the posterior longitudinal bundle formation, and of a far less pronounced character than those occurring after lesion of the vestibular complex.

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[1] It will be shown, in a subsequent paper, that the forced movements in a plane vertical to the longitudinal axis of the animal, such as staggering and tumbling, are also controlled by similar nuclei and tracts. Wallenberg's basal olfactory bundle and its fibres joining the posterior longitudinal bundle and Tschermak's (from the central median nucleus?) ascending fibres in the same fascicle are not taken into consideration in this study.

This I formerly held to be due to the fact that the degeneration of the nerve-sheaths progresses at a certain rate, and the stimulation necessary for the production of those forced movements, being dependent on this degeneration, is naturally more transient the nearer the lesion is to the end station. It is interesting to note that, according to the statement by Kohnstamm and Quensel [80], the tigrolytic action is better marked the nearer the lesion of the axis-cylinder is to the end station. Since, however, I got convincing proof, from experiments in the thalamic region, that the forced movements of a longer duration are probably always due to a deficiency of the nerve influences on the one side and the unantagonized action of the analogous structures on the other side, a simpler explanation offers itself. It is this, the functional arrangement of the ascending vestibular system is such that the further the lesion is from the vestibular region the more easily and completely does the compensatory mechanism step in. This holds good particularly for rolling movements. We are not, however, prepared to give anatomical data in support of this generalization.

Secondly, it appears evident that in the higher mammals in a series of lesions, from below upwards, the direction of both forced movements changes abruptly as soon as the region of the posterior commissure is reached. In the lower animals (fishes and reptiles), on the other hand, forced movements are absent after lesions lying higher in the cerebrospinal axis than that commissure.

I held formerly that this change of direction of forced movements in higher mammals was due to the fact that the major irritation which is dependent on the ascending degeneration of the above mentioned tracts, and which acts by means of the posterior commissure on the heterolateral reflex centre, is put out of action, while the weaker stimulus of the descending degeneration of the commissuro-medullary and the interstitio-spinal tract comes into force. Later observations in lower animals led to the belief that in these simpler creatures the ascending vestibular system stops short in the mesencephalon ; where, as in the higher ones, the superimposed reflex centres are linked to newly acquired neurons in the striate body, thalamus and pallium (Ariens Kappers [3]). Hence in reptiles ablation of a cerebral hemisphere causes no circus movement to the side of lesion, nor does faradic stimulation of the striate body cause conjugate deviation of head and eyes to the other side, as it does in all higher vertebrates, including birds.

Chapter VI.—Forced Movements after a Lesion in the Mesencephalic and Thalamic Regions; the Superimposed Reflex Arc and its Afferent Systems.

As regards the constituents of the posterior longitudinal bundle formation, fresh evidence is afforded by the former chapters in support of the view taken by other workers that this bundle contains centrifugal as well as centripetal bundles, and further arguments are brought forward that these centrifugal tracts control the equilibrium of movement in two planes.

It appeared probable that the commissuro-medullary bundle is the carrier of the centrifugal limb of the superimposed reflex mechanism concerned with the circus movements, while the interstitio-spinal tract is considered the centrifugal one for the rolling movements.

In the controversy on the anatomical side of this subject, between Cajal [40] and de Lange, as to the mesencephalic descending fibres passing into the posterior longitudinal bundle formation certain statements made by both authors may be taken as correct. For example, Cajal describes a strand of fibres passing downwards from the interstitial nucleus in the innermost portion of the posterior longitudinal bundle, while de Lange [86] describes a similar strand of descending fibres in the same part of the posterior longitudinal bundle, but shows that it originates in the nucleus of the posterior commissure. As we have seen in Chapters II and IV, we deal here with two different tracts, each having its own origin and termination, the fibres from the interstitial nucleus passing far down into the cord, while those from the nucleus of the posterior commissure do not extend beyond the medullary region. Arguments are also brought forward to prove that the two tracts subserve different functions. From a study of the results following different lesions in the hypothalamic region and mid-brain, it would appear that forced movements which persist, mostly occur when the region of the nucleus interstitialis and the nucleus of the posterior commissure is injured. In such cases the tracts just described are more or less degenerated.

With these facts to go on one is led to a different conclusion from that arrived at by Boyce [28], who, in discussing the forced movements and positions, observed after similar lesions, remarked, "It would of course be difficult, with the slight knowledge before us, to attempt an explanation of these phenomena"; Probst's similar opinion was expressed in 1900 [124].

Sufficient advance has been made in recent years in our knowledge of the minute anatomy of the brain, thanks to the London, Vienna, Paris, Frankfort, Madrid and Amsterdam[1] schools of anatomy, to ascertain some details of the anatomical structure of both the peripheral and superimposed vestibular reflex arcs. Two peripheral arcs on either side may deal with the compensatory movements in both the horizontal plane and the plane vertical to the long axis. Ascending fibres pass from those double systems to the mesencephalic or hypothalamic nuclei. The arrangement of the fibres, moreover, which pass to those nuclei from the posterior commissure and the cerebral hemisphere is such that a lesion of the nuclei, or of the region immediately oral and lateral to them, is followed by a change in the direction of the forced movements.

The question now arises, have we sufficient anatomical knowledge to trace out accurately the course of these secondary ascending vestibular fibres into the mesencephalic nuclei? It must be frankly admitted that the present methods for staining medullated nerve-fibres are inadequate.

In the case of rolling movements it is even more difficult to demonstrate a complete reflex arc than for circus movements. In the schematic drawing appended the vestibulo-mesencephalic tracts, which control the circus movements centripetally, terminate near the posterior commissural nucleus. So far, my efforts to trace the vestibulo-tegmental tract up to its nodular point have failed, although the nucleus interstitialis has been demonstrated, as far as this physiologically seems possible, as controlling the rolling movements centrifugally. It must, however, be remembered that the Marchi method, which was used, is only effective with myelinated nerve-fibres.

In order to judge by means of a method that brings the non-medullated nerve-fibres to evidence, about the anatomical connexions of the commissural nuclei (nuc. commissur. post. and nuc. interstitialis), I have, with Dr. Bok, carefully examined frontal and sagittal series of sections through chicks' brains, stained after Cajal's silver method. It was easy to confirm Cajal's statement that the majority of neurites descend into the posterior longitudinal bundle, but besides that we found not rarely the axons take a direction towards and into the posterior commissure (ventral division). We saw no axons take an oral direction, but convinced ourselves that the dendrites of a good number of cells of the nuc. commissuræ posterioris are directed towards the oral and ventral parts. This suggests accepting the theory, defended by Tretjakoff and other anatomists, that the dendrites grow out towards the side from which the impulses arrive—that a good number of centrifugal striatal connexions exist in the chick at least that innervate the nuclei in question.

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[1] Personally I feel particularly indebted to Dr. Ariens Kappers for his permission to use his private anatomical library and that of the Dutch Central Brain Institute, and to Prof. C. Winkler, and also Dr. van Valkenburg, for having more than once looked into my series of specimens, and to all of them for having given useful suggestions.

For the anatomical details of the mesencephalic nuclei themselves I must refer to the masterly description given by Ramon y Cajal [40] and to the work of Dejerine [44], who considers that they belong to the ganglia of the central grey matter. In my own investigations I have found, even in selachians, the characteristic large cells of the interstitial nucleus which spread over a large area, and the more definitely localized small-cell nucleus of the posterior commissure.

Passing next to the consideration of the physiological significance of the parts oral to those nuclei, we find that we must confine ourselves to the higher vertebrates, since only in this class does a lesion of the mesencephalic nuclei and the tracts cephalic to them cause forced movements at all, the direction of the movement being opposite to those associated with unilateral lesion of the posterior longitudinal bundle. In this connexion it is interesting to find that all authors are in agreement; in fish and amphibians (Steiner [153, p. 83]), reptiles (Fano [53] and Bickel [20]), and birds, ablation of one cerebral hemisphere is not associated with the development of forced movements. My own experiments, which deal particularly with cats, are in complete agreement with those of Schiff [144], who stated that no local cortical lesion is followed by circus movements which continue for any length of time. A lesion of the deeper parts, such as the striate body or the lateral parts of the thalamus, is, however, followed by circus movements, and conjugate deviation of the eyeballs towards the side of the lesion. This condition may persist for a longer period. It is interesting to note that the circus movement towards the side of the lesion is usually accompanied by a slight rotation round the bodily axis towards the non-operated side. This fact was also noted by Prévost [122]. From an examination of my own material I find in these cases a strand of degenerated nerve fibres, which runs in a latero-median and slightly antero-posterior direction through the external medullary lamina, spreads out in the field of Forel, and disappears near the frontal part of the red nucleus (figs. 15*a* and 15*b*).

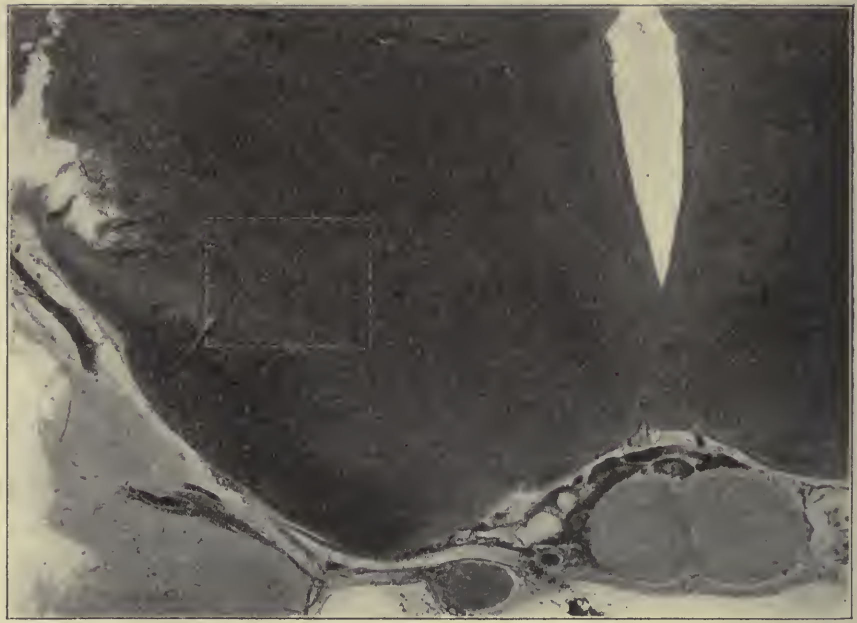

Fig. 15*a*.

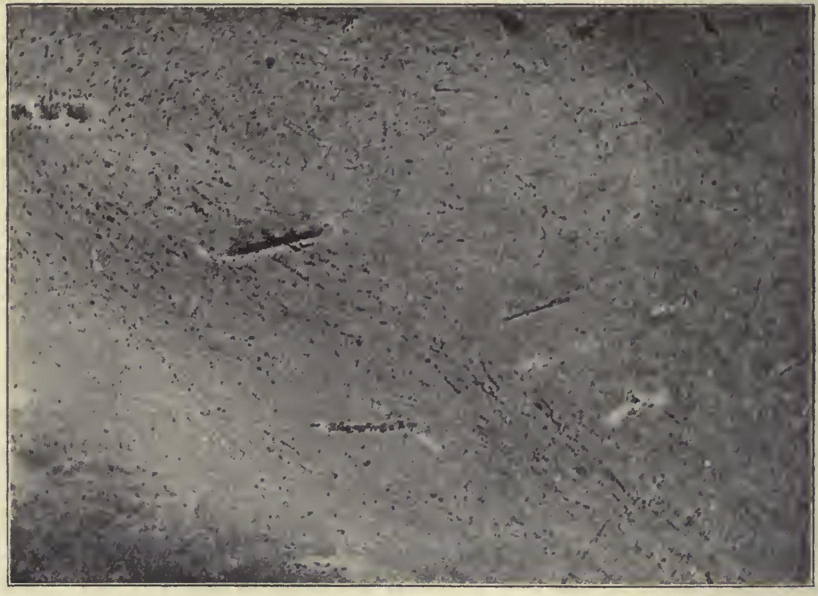

Fig. 15*b*.

Figs. 15*a*, 15*b*.—Cross sections from cat 186.

Fig. 15*a*.—Region of the lesion. Destruction on the left side of the ventral part of the striate body.

Fig. 15*b*.—Magnified portion of fig. 15*a*. Note degenerated strand of fibres in the lamina medullaris externa.

This strand of fibres lies therefore in the same region in which Dejerine [45], Probst [125], and Roussy [135] find that a large number of fibres disappear after lesion of the lateral parts of the optic thalamus.

The first question now is where do those fibres go to?

It is interesting to note that Sachs [140], working in Sir Victor Horsley's laboratory, reported the case of a rhesus, where the lesion lay in the external medullary lamina, and which showed a similar strand of degenerated nerve-fibres. This author believes that those fibres terminate in the red nucleus. From the evidence already discussed, it seems to me more probable that they terminate in the nucleus of the posterior commissure, and, from Bernheimer's experiments, possibly in the interstitial nucleus of the opposite side. This view is further supported by another case reported by Sachs in which the lesion was in the field of Forel; the same bundle of fibres was degenerated, while some fibres in the posterior longitudinal bundle of the same side also showed degeneration, proving that the interstitial nucleus (at least cells, from which the posterior longitudinal bundle fibres originate) was involved in the lesion.

Where does this bundle of fibres described by Sachs [140] and myself originate?

Up to the present time no conclusive evidence on this point has been furnished by our experiments. At the same time I make the suggestion that their origin lies either in the globus pallidus or in the putamen. This theory is suggested by the fact that in none of my cases of lesion involving the cortex alone were these fibres found degenerated, but only when the deeper parts such as the striate body or the lateral parts of the thalamus were involved. It is further supported by the work of Sachs [140], who succeeded in tracing a thalamo-fugal tract, lying in the same situation and following the same course, from the external medullary lamina to the globus pallidus. The data afforded by the pathological cases discussed in Chapter VII, together with the anatomical data supplied by v. Bechterew [11], Ariens Kappers [3] and de Vries seem also to support this theory.

As regards the physiological significance of this bundle the experiments of Horsley, Sachs and Clarke [41] appear to speak in the same sense. They tend to prove that faradic stimulation of the posterior third of the lateral nucleus thalami, that is the region in the immediate neighbourhood of the external medullary lamina, causes deviation of head and eyes to the opposite side. My observation quite fits in here. Section of the bundle causes circus movements and conjugate deviation to the side of the lesion. Turning to the records given by other workers I find no arguments against my view in the cases given by Probst [125] and Roussy [135]. The older work of v. Monakow [104] and Mingazzini [101] is not suitable for application of this problem, since the brains were not examined by the Marchi method. In some of the older work by Ferrier and Yeo [56] dealing with suboccipital lesions, and in one of Schäfer and Horsley's experiments [142, Case 6], observations of forced movements occurring after lesion of the region under discussion are recorded. These movements consisted of conjugate deviation to the side of the lesion, falling to one side, or rotation of the head towards the uninjured side.

It is now interesting to see whether any of the old ablation or stimulation experiments, carried out when the present anatomical knowledge had not been arrived at, serve to confirm or deny the views put forward in this paper. The experiments by Adamuk [2] and Topolanski [155] are extremely interesting since the gross resections of the brain-substance indicate fairly accurately that our commissuro-medullary and interstitio-spinal tracts, and also the ascending fibres of the posterior longitudinal bundle, are the elements the destruction of which destroys the co-ordinated ocular movements induced by electrical stimulation of the brain-stem.

So easily were those movements elicited even with slight currents that Knoll [79] suggested that a good many of the results of the stimulation experiments of the cerebral cortex really depended upon current loops [cf. Mott, Schuster and Sherrington, 105]. It will be recalled that Ferrier [54], Schäfer [142], Horsley [14], Beevor and Vogt successfully elicited conjugate deviation of the head and eyes by stimulation over a large frontal area, while Bernheimer [15] and Levinsohn got the same results by stimulating other areas.

From the clinical point of view Landouzy [85] and Grasset long ago pointed out that in disease of the hemisphere conjugate deviation of the head and eyes towards the lesion is due to the paralysis of those structures which on faradic stimulation cause conjugate deviation towards the opposite side. Whether the voluntary impulses from the cerebral cortex, which are associated with forced movements or conjugated lateral movements of the eyeballs, are at all times transmitted through the centrifugal limb of the superimposed reflex arc, as described in Chapter III and in this chapter, must in the meantime remain an open question. It may be, however, admitted that the results of Munk [106] and Levinsohn [88] support this suggestion. Further, in the light of our results, it seems highly probable that Bernheimer [15] is right in believing that these impulses must travel along paths situated on the ventral side of the sylvian aqueduct.

My experiments, taken in conjunction with those of Horsley and Sachs, lead to the supposition that the inner portion of the lenticular nucleus and its connexions with the nuclei of the posterior commissure are associated particularly with the conjugate deviation of the head and eyes towards the side of the lesion in the case of destruction, and towards the other side with electrical stimulation. Also Ferrier [54] found in the genu of the striate body a centre, electrical stimulation of which caused conjugate deviation from the side of stimulation.

Clinical and anatomical observations also tend to corroborate this view. Uhthoff [157], in his interesting article dealing with a series of anatomical lesions in the cerebral hemisphere in man which had caused conjugate deviation during life, describes the lentiform nucleus, claustrum, internal capsule, optic thalamus, and caudate nucleus as being most frequently involved. Prévost and Broadbent had made similar remarks before. Hösel [72] also found that one of the first tracts to become medullated is that which connects the region anterior to the red nucleus with the globus pallidus.

All this independent evidence seems to urge the necessity for a further investigation on the relationship between strial and cortical influx and the conjugate deviation of the head and eyes, from the newly acquired points of view.

Chapter VII.—Conjugate Deviation of Head and Eyes, and Different Forms of Nystagmus in Clinical Neurology. Their Localization Value.

The physiological analysis of the posterior longitudinal bundle formation has undoubtedly an important bearing on the clinical problem, afforded by the conjugate deviation of both eyes in cerebral disease generally, and particularly in pontine disease involving the sixth nucleus. Unless the physiological analysis of this formation be taken into consideration it is impossible to explain the additional conjugate deviation of the heterolateral rectus internus, with the rectus externus of the diseased side in an organic affection of the sixth nucleus. Foville [58], Hughlings Jackson [74], Duval, Wernicke [166], Bleuler [25], Bruce [37], Bischoff, Spitzer [149] and others, accept the view that the nervous influx for the lateral movement of both eyes descends to the sixth nucleus and ascends to the third nucleus; they also consider that there is a recrossing of the pyramidal fibres dealing with this movement.

Many authors have felt the difficulty of accepting this somewhat improbable supposition, for which there is further no anatomical basis. If, however, the forced movements in the horizonal plane and the closely associated conjugate deviation in the same plane be carefully considered in the light of the above data, it is evident that there is no need to fall back on this theory.

A full discussion on this subject will be reserved for a later communication, but it may be said here that, after a careful scrutiny of the writings, hardly a case is found where there is not a lesion in the posterior longitudinal bundle formation as well as in the sixth nucleus.

If we consider the conjugated deviation [107, p. 216] as a minor degree of circus movement as well as a part of it, it is seen that this conjugate deviation of head and eyes in pontine diseases to the non-affected side is closely related to the circus movement towards the normal side, seen after one-sided lesion of the posterior longitudinal bundle formation between Deiters' nucleus and the posterior commissure in our experiments.

It is quite natural that in primates this forced movement, with conjugate deviation of the head and eyes, associated with pontine lesion, is to a greater extent under the power of the will than in the case of the lower vertebrates, a more or less continuous effort being made to counteract it. In fact, in the monkey it is rare to find a regular circus movement associated with a conjugate deviation to one side. In any case it never amounts to more than a slight circus movement, such as is seen in cats just before the symptom disappears, which passes, leaving a tendency to conjugate deviation of the head and eyes. Even conjugate deviation is overcome in primates with a certain ease. So it is that Munk [106], Ferrier and Yeo, as also Hunnius and Bernheimer, rightly insist that an unwillingness to look to one side must be looked for in the proper cases. Indeed, circus movement and conjugate deviation of the eyeballs in the horizontal plane, e.g., to the right side, and unwillingness to look to the left side, are all different degrees of the same fundamental phenomenon. It is therefore not surprising to find the heterolateral eyeball in pontine disease of man deviated inward, since a lesion of the eminentia teres and the sixth nucleus by virtue of its vicinity to the posterior longitudinal bundle involves this bundle also. In this connexion the cases recorded by Rickards [131], Wiersma [167], Bristowe [33], Byrom Bramwell [30], Bruce [37], and Hunt should be examined.

It is only in cases of pontine tumour with no involvement of the posterior longitudinal bundle, but affection of the sixth nerve, that the internal rectus muscle of the other side may be expected to act normally. Reference may here be made to the work of Graux [67], Bennet and Savill [141] and others.

Regarding conjugated deviation in disease of the hemisphere, Wernicke's case [166] has long been regarded, in the German literature, as decisive proof that in man the angular gyrus is a special centre for this deviation. Destruction of this centre has long been supposed to cause conjugate deviation towards the side of the lesion, while irritation of the centre is associated with deviation towards the other side. This theory found support in the fact that in monkeys stimulation of the angular gyrus with the faradic current causes conjugate deviation to the opposite side. A careful scrutiny, however, of the anatomical findings of this case and of Prévost's [123] classical work, and Broadbent's cases [34], taken in the light of our observations on the superimposed vestibular reflex arcs, leads to the conclusion that there is considerable doubt on this point (Klaas). In Wernicke's case the third zone of the lenticular nucleus was involved as well as the cortex of the angular gyrus. This part of the striate body can therefore not be discarded as a centre in connexion with which the symptom of conjugate deviation arises.

Stimulation of the human cortex by minimal faradic currents has never, in my experience, been associated with conjugate deviation, nor, so far as I am aware, have Horsley, Krause or Cushing recorded this result. Unipolar stimulation is for several reasons, already pointed out in this paper, unsuitable for this purpose. For the present, therefore, it seems to me that the localizing value of the hemispheral conjugate deviation must remain *sub judice*. At the same time, I think that the ocular symptoms which occur in cases like No. 11 of Oppenheim's series [119] where the lenticular nucleus is involved, are worthy of considerable attention. If, in addition to paralysis of the nucleus abducens of the one side, there are indications of some paresis of the internal rectus muscle of the opposite side, when both are brought into action simultaneously, the condition may be diagnosed as conjugate deviation to one side or as defective movement to the opposite side. It must not be regarded as a secondary pressure symptom.

It is interesting to note how clinical observations, quite apart from physiological research, have led to the appreciation of the fact that a destructive lesion of the cerebral hemisphere and optic thalamus is associated with conjugate deviation to the side of the lesion, and that a similar unilateral lesion in the pontine region causes the same deviation from the side of the lesion.

Long ago Grasset and Landouzy stated, "Dans les lésions de l'hémisphère le malade regarde ses membres convulsés, s'il y a excitation, et regarde sa lésion, s'il y a paralysie. A partir d'un certain point mal défini, à la limite des parties supérieures et moyennes de la protubérance, la formule doit être renversée." D'Astros [4] writing in 1894, considers it impossible to localize this "reversal point."

As a result of the observations now recorded there seems to me to be little doubt but that this point is situated in the posterior commissure, probably in the nucleus, both in man and in the lower type of mammal exemplified in the cat.

The question of the exact topographical distribution of conjugate deviation in the frontal and occipital regions dealt with by Ferrier, Schäfer, Horsley, Marina [100], and that which is discussed in the controversy between Luciani [96] and other workers, seems to me to be, after what has been said above, only of secondary interest. Regarding cerebellar disease, I may recall the fact, dealt with in Chapter II, that forced movements were never associated with my experiments involving lesions of the cerebellar cortex, or of the dentate nucleus [8].

The question which Bonnier [27], Launois, Chèze and others have attempted to answer as to whether a special Deiters' syndrome can be recognized in pontine disease, also lies outside this paper.

It is quite evident from what has been said regarding forced movements in quadrupeds that very careful distinction must be made in man between deviation in the horizontal plane and falling to a side. As regards the latter phenomenon it seems certain, from the work of Marburg [99], that besides the falling movements towards the medullary lesion the same movement towards the normal side is not infrequently observed. This latter condition is in agreement with the results got in my experiments on the ramus descendens of the vestibular nucleus. For the most recent observations on this subject I must refer to the second case recorded by Wallenberg [161], to the work of Schwarz [146] and to the case of thrombosis of the posterior inferior cerebellar artery recorded by Goldstein and Baum [64]. It seems, however, to be the general rule in man, as in the cat, that a lesion of the vestibular nerve-roots and of the more oral parts of Deiters' complex are associated with falling to the side of the lesion. This phenomenon of falling to the side must be specially examined in man since the erect posture makes it impossible to bring it quite into line with the còndition as it occurs in quadrupeds, where it really is a minor degree of the rolling movements.

From my observations [107, 113] on the direction of the different forms of nystagmus found associated with lesion of the hind-brain which have been confirmed and extended by Bárány [6], there can be little doubt but that the mechanism in such cases is as complicated as that described for the forced movements, and that the two mechanisms are closely related. I will merely recall that some authors (Marburg and Bartels) believe that the rapid and slow jerk seen in vestibular nystagmus have different localization.

In my experiments the slow jerk of the nystagmus accompanying the forced movements and forced position of the eyeballs always took the same direction as that in which the eyeballs were deviated. In lesions of Bechterew's nucleus and the homolateral vestibulo-mesencephalic tract in the posterior longitudinal bundle, the slow jerk of the horizontal nystagmus is directed towards the uninjured side. If the lesion be situated in the right vestibular root and the right Deiters' nucleus proper then the slow jerk of the nystagmus, associated with this condition, accentuated the already existing divergent squint, the right eye being directed downwards, the left eye upwards. Do these facts justify us in deducing diagnostic points for use in localizing the lesion in cases where one-sided nystagmus is present, but where, as is not infrequently the case in subtentorial lesions, forced movements or conjugate deviation are both absent? It seems to me that this is a point worthy of further consideration, but my own experience furnishes no conclusive evidence on the question.

Generally speaking, this anatomical and physiological research tends to show the importance of accurate clinical observation of even slight defects in the co-ordinated ocular movements in brain disease. Some of these lesions and their accompanying symptoms are as follows: A lesion anywhere from the descending ramus of the eighth nerve up to the striate body is liable to cause certain disturbances. In man these disturbances are more commonly in the horizontal plane, and are at present so little understood that only a rough outline can be given of the pathological conditions which possibly induce the symptoms.

A *destructive* lesion of the posterior longitudinal bundle on the right side of the brain between the vestibular region and the posterior commissure is liable to cause conjugate deviation of the head and eyes to the left side, or else incomplete lateral deviation to the right side. If this symptom occur when the lesion is oral to the posterior commissure it is indicative of an organic destructive lesion on the left side. If there is conjugate deviation of head and eyes to the left side, and an *irritative* lesion, cephalad to the posterior commissure is probable (eventually convulsions of muscles on the left side), the irritative lesion may be localized in the thalamus and striate body on the right side.

If the symptom of Magendie-Hertwig squint (right eye directed downwards, left eye upwards) occur either alone or concurrently with conjugate deviation of the head and eyes, or if there is a tendency to fall or lie down on the right side, then the lesion (if situated in the medulla or truncus cerebri) probably has involved the vestibulary region or the lateral part of the posterior longitudinal bundle on the right side. If this symptom is present where the disease is localized cephalad to the posterior commissure, then, from experimental findings, the lesion is to be localized in the optic thalamus or striate body on the left side. If a destructive lesion is situated in the vestibular or cerebellar regions, and there appears deviation of the head and eyes to one side, for instance the left, we deal either with a conjugate deviation in the horizontal plane to the *left*, or with a condition allied to the rolling movement to the *right*. A careful searching for the Magendie-Hertwig squint (left eye down, right eye up) or a tendency to lie down on one side (the left) or a divergent nystagmus, slow in the sense of the deviation, will enable us to diagnose a condition allied to rolling movements to the right. Since unilateral cerebellar disease is very liable to affect the vestibular nerve and Deiters' nucleus, it is clear why in this type of case there is frequently a tendency to lie down on the diseased side. It is only in cases where the ramus descendens of the eighth nerve is involved that one is likely to get exceptions to this rule.

After what has been said, it need hardly be pointed out that Bruns' symptom of disequilibration in frontal tumour [38] cannot be discussed, unless the above observations be taken into consideration.

In examining for ocular deviation the voluntary and automatic deviation of the eyeballs must be tested separately. Wernicke [166] states that Tiling long ago pointed out that reflex deviation, such as is seen when a moving object is followed by the eyes, may be demonstrated while voluntary lateral deviation is lacking. Bielschowsky [22] further emphasized the importance of this fact in routine examination. The symptom of "Vorbeizeigen" in cerebellar disease observed by Bárány may, I think, be due entirely to involvement of the vestibular structures. The fact that horizontal nystagmus is never accompanied by a tendency to fall to one side is quite readily understood when the mechanism of the two types of forced movements is taken into consideration.

The observation that a large percentage of deaf people do not suffer from dizziness, as noted by James and Kreidl, and further, that in very young infants sea-sickness does not occur, seems to indicate that there is some connexion between those conditions and imperfect functioning of the vestibular complex, either peripherally or centrally. The experiments of Nagel [118], Bishop Harman [24], Quix [129], Bartels and Rothfeld [132] render it extremely probable that the compensatory movements of the eyeballs in different movements of the head, and also the reflex adjustment of the eyes in vertical and other directions during rotation, are dependent on the labyrinthine reflexes. Where there is, e.g., circus movement or conjugate deviation to the right side, the compensatory deviation to the contralateral side during and after rotation are found absent. Reddingius, Marina [100], F. B. Hoffmann, and Bielschowsky have investigated the question of the reflex adjustment of the eyes in vertical and other directions during ocular movements; these reflexes will probably be proved to be equally dependent on a normal activity of these reflex mechanisms and their conduction by the posterior longitudinal fascicle [cf. Cajal, 40, i, p. 728].

In the case of octopods [110], it has been shown that the reflex adjustment of the eyeball by the otolithic organ is in this animal predominantly homolateral; by this reflex the pupillary slit is maintained in the horizontal position in practically all the positions assumed by the body. A similar condition seems to exist in the python, as here also the pupillary slit is held constantly vertical.

The very delicate muscular adjustment of the eyeballs in the higher vertebrates which is necessary, according to Mulder, Nagel [118], Hering and Bielschowsky, for the localizing of the visual field to the same part in the two retinæ in all changing positions of the head, is probably also a vestibular reflex system; the innate tendency to fuse the two visual fields, even when anatomical or nervous defects exist, also plays an important part. The work of Marina on this subject is worthy of attention.

SUMMARY.

In reviewing this physiological analysis of the vestibulary system and the posterior longitudinal bundle formation, certain facts, both physiological and anatomical, stand out clearly, while other points can only be considered as suggestions or probabilities.

(1) The study of the physiological phenomena observed after lesions of different parts of this system demonstrates that there is a far-reaching differentiation of function in the primary end-stations of the vestibulary nerve. Further, it also shows that the different strands of fibres which connect the vestibular nuclei with the various nuclei in the mid-brain and with the region of the posterior commissure in a cerebro-petal direction may be more accurately analysed.

(2) The principal vestibular nuclei are the following: (*a*) The descending branch of the vestibular nucleus; (*b*) Deiters' nucleus composed of a ventral caudal division, named the nucleus triangularis, and a dorsal magnocellular division or Deiters' nucleus proper; (*c*) Bechterew's nucleus with the nucleus tecti.

(3) Physiological analysis affords a practical method of establishing the existence of important differences in the ascending and descending connexions of the above-mentioned nuclei, and of establishing equally important differences in the functions of the nuclei.

(4) The starting point of this analysis is the fact that an ascending degeneration of the crossed vestibulo-mesencephalic bundle, which forms the bulk of the mesial part of the posterior longitudinal bundle till near the nucleus of the posterior commissure, is always found associated with circus movements to the side of the intact posterior longitudinal bundle. This rule holds good so long as the lesion leaves the other parts of the vestibular systems intact. It is immaterial whether the degeneration of this vestibulo-mesencephalic tract is the result of a cross section of the median part of the posterior longitudinal bundle, or of a lesion of the heterolateral Deiters' nucleus. Experimental evidence tends to show that in the Deiters' complex the nucleus triangularis is the principal origin of this tract (fasciculus vestibulo-mesencephalicus cruciatus).

(5) The degeneration of an ascending tract lying immediately lateral to the crossed vestibulo-mesencephalic tract in the posterior longitudinal bundle formation appears to be equally associated with a circus movement (or rather conjugate deviation) to the side of the normal posterior longitudinal bundle. This tract is further shown to be a homolateral tract originating exclusively in the nucleus of Bechterew,

at least in the oral parts of the vestibular region, and terminating in the region of the posterior commissural nucleus. This bundle may be styled the homolateral vestibulo-mesencephalic fasciculus.

This tract is only partially identical with that described anatomically by Probst [124]. Van Gehuchten [63] in 1904 suggested that the whole of the lateral part of the posterior longitudinal bundle (fasciculus Deiters' ascendens, Lewandowsky, Winkler [169]) consisted of fibres, ascending from Bechterew's nucleus. This origin, for this limited portion at least of the posterior longitudinal bundle, may now be held as proved [cf. 108], as may also the association of its upward degeneration with circus movements or conjugate deviation to the normal side.

Both the circus movements observed after lesion of the homolateral or crossed vestibulo-mesencephalic tracts are associated with conjugate deviation of the head and eyes to the side of the movement, or with loss of lateral deviation of the eyeballs to the opposite side.

(6) According to the notions advanced by Duval, Bleuler, Edinger, Bischoff, Spitzer, Kohnstamm, Bernheimer, Fraser, Wallenberg, Wiersma, and others, the posterior longitudinal bundle represents a combination of ascending and descending tracts, which control the co-ordinated movements of the eyes, head, and trunk, and control or direct the maintenance of the equilibrium of motion. Now, from experimental data furnished by the present investigation, it is seen that after a direct lesion in the region of the posterior commissure of the cat on one side, where the resulting circus movements were directed to the side of the lesion, a descending tract degenerates which lies at the innermost part of the posterior longitudinal bundle of the same side. This tract probably originates in the posterior commissural nucleus. As it stops short in the medulla it is suggested that it may be termed the fasciculus commissuro-medullaris [cf. 108].

(7) Although it is probable that this mesencephalo-medullary tract exists in all the higher organized vertebrates such as selachians, teleosteans, amphibians, reptiles, birds and mammals, it is only in the mammal that a destructive lesion of the nucleus and of its efferent tracts from the striate body is associated with circus movements towards the side of the lesion. In the lower animals a lesion oral to the posterior commissure is not followed by any circus movements.

The anatomical explanation of this fact seems to be that only in mammals are the hypothalamic and commissural nuclei sufficiently connected with the prosencephalon that section of the connexions should be followed by asymmetrical locomotion, as evidenced in circus movements and conjugate deviation towards the side of the lesion. Further, it is only in mammals that stimulation of certain definite areas of the cortex is followed by conjugate deviation of the head and eyes towards the opposite side. Birds seem to form in this respect a group between the reptiles and mammals. In the prosencephalon of the bird is an area, faradization of which is associated with conjugate deviation towards the opposite side (Boyce and Warrington). The section of the connexions of this area is not, however, associated with any alteration in the mode of locomotion. As regards those cases (cats), where, after lesion of the thalamus and cerebral hemisphere, circus movements towards the side of the (destructive) lesion were observed over a longer period, it was found that there was a tract of degenerated fibres in the lamina medullaris externa. These fibres, which probably emanate from the striate body, pass to the hypothalamic region, where they lose their medullary sheaths. The termination of these fibres, probably in the nucleus of the posterior commissure, can, therefore, not be demonstrated. The circus movement in such cases is always accompanied by conjugate deviation towards the side of a destructive lesion, or in less pronounced cases by loss of lateral deviation to the other side.

(8) Like the circus movements the rolling movements may serve as a guide in working out the anatomo-physiological analysis of the vestibular complex and the posterior longitudinal bundle formation.

(9) After a direct lesion of the complicated nerve-fibres, which help to form the vestibular root, a rolling movement towards the injured side is constantly observed, mostly associated with a skew deviation and conjugate rotation of the eyeballs around their antero-posterior axis. In only one case (rabbit, direct lesion in the caudal part of the vestibular root) were rolling movements towards the non-injured side observed.

(10) In three cases of lesion of the descending branch of the nucleus vestibularis rolling movements towards the normal side were seen lasting over several days. Although this experiment was repeated several times, I failed to localize any distinct ascending or descending connexions from this part of Deiters' complex.

(11) Lesion of Deiters' nucleus proper is found in two cases associated with rolling movements, moderate in character, towards the side of the lesion. From this nucleus the degeneration spreads upwards along a tract which lies in the outermost part of the lateral horn of the posterior longitudinal bundle. A direct lesion of this ascending tract or connexion is also associated with a tendency to roll towards the side of the lesion. This was demonstrated in five cases.

The fibres of this tract appear to end mostly in the tegmentum, although some may be traced to the caudal part of the posterior commissure, where the fibres appear to lose their medullary sheath ; it is therefore suggested that it should be styled the tractus vestibulo-tegmentalis lateralis. Its origin is apparently in the medium-sized cells of Deiters' nucleus proper, its termination probably in the interstitial nucleus.

(12) A comparison of the cases where the lesion is situated in the region of the posterior commissure leads us to postulate in that region a centre, probably the nucleus interstitialis, injury of which (or of its afferent tracts from other parts) in the cat is constantly followed by rolling movements to the normal side. The existence of a descending interstitio-spinal tract in the innermost section of the posterior longitudinal bundle in these cases in which rolling movements or, in less pronounced cases, a tendency to fall to the normal side are observed seems to justify this supposition to a certain extent.

(13) The physiological combined with the degenerative method does not afford such ample information as regards the tracts from Deiters' complex to the posterior longitudinal bundle formation of the spinal cord. This is partly due to the irregular form of the collection of reticular cells which give rise to the ponto- or reticulo-spinal tracts. It seems certain that heterolateral descending fibres of the posterior longitudinal bundle do not come from Bechterew's nucleus, although descending homolateral fibres are given off from both Deiters' and Bechterew's nuclei. After experimental lesion of Deiters' nucleus it was not in all cases possible to decide from what cells the heterolateral fibres originate. If the descending connexions of the vestibular structures which control the circus and rolling movements and those of the superimposed mesencephalic structures be compared, the conclusion seems warranted that the descending connexions are far more important in the case of the rolling movements. Relatively few descending fibres which originate in the structures associated with circus movements pass beyond the sixth nucleus.

BIBLIOGRAPHY.

[1] D' ABUNDO. *Arch. Ital. de Biol.*, 1910, t. liii, p. 321.

[2] ADAMUK, E. *Centralbl. f. d. med. Wissensch.*, 1870, S. 65.

[3] ARIENS, KAPPERS. *Anat. Anzeig.*, 1908, Bd. xxxiii, S. 321.

[4] D'ASTROS. *Rev. de Méd.*, 1894, t. xiv, p. 152.

[5] BABINSKI, J. *Rev. neurol.*, 1902, t. x, p. 1012.

[6] BÁRÁNY. "Vestibular-apparat," Berlin, 1906, S. 14.

[7] *Idem.* *Wien. klin. Wochenschr.*, 1912, Bd. xxv, S. 2023.

[8] BATTEN. *Brain*, 1906, vol. xxix, p. 494.

[9] BECHTEREW, W. v. *Deutsche Zeitschr. f. Nervenheilk.*, 1900, Bd. xvii, S. 221.

[10] *Idem.* *St. Petersburger med. Wochenschr.*, 1882, Bd. vii, S. 97.

[11] Bechterew, W. v. "Physiologie d. Nervensystems," Jena, 1908, Heft ii, S. 1119.
[12] *Idem.* *Pflüger's Archiv*, 1883, Bd. xxxi, S. 479.
[13] *Idem.* "Leitungsbahnen," Leipzig, 1899, p. 295.
[14] Beevor, C., and Horsley, V. *Phil. Trans. Roy. Soc.*, 1887, vol. clxxviii, p. 153.
[15] Bernheimer. *Arch. f. Ophth.*, 1903, Bd. lvii, S. 363.
[16] Bertelsen und Rönne. *Monatsschr. f. Psychiat. u. Neurol.*, 1909, Bd. xxv, S. 148.
[17] Besta, C. *Arch. f. Psychiat.*, 1913, Bd. l, S. 323.
[18] Bethe. *Pflüger's Archiv*, 1899, Bd. lxxvi, S. 470.
[19] Biach und Bauer. *Obersteiner's Arbeiten a. d. Neurol. Inst. Wien*, 1911, Bd. xix, S. 56.
[20] Bickel, A. *Arch. f. Anat. u. Physiol.*, 1901, S. 56.
[21] Biehl. *Obersteiner's Arbeiten a. d. Neurol. Inst. Wien*, 1907, Bd. xv, S. 71.
[22] Bielschowsky. *Monatsschr. f. Psychiat. u. Neurol.*, 1909, Bd. xxv, S. 267.
[23] *Idem.* *Deutsche Zeitschr. f. Nervenheilk.*, 1902, Bd. xxii, S. 54.
[24] Bishop-Harman. *Journ. of Anat. and Physiol.*, 1900, vol. xxxiv, p. 27.
[25] Bleuler. *Deutsche Arch. f. klin. Med.*, 1885, Bd. xxxvii, S. 27; *ibid.*, 1885, Bd. xxxviii, S. 28.
[26] Bolk, L. "Petrus Camper," Bd. iii, Aufl. 1, Blz. 28.
[27] Bonnier, P. *Presse Méd.*, 1903, t. xi, p. 861.
[28] Boyce, R. *Phil. Trans. Roy. Soc.*, 1895, B., vol. clxxxvi, pp. 335 and 361.
[29] Boyce and Warrington. *Ibid.*, 1899, vol. cxci, p. 308.
[30] Bramwell, Byrom. *Edin. Med. Journ.*, 1909, n. s., vol. ii, p. 129.
[31] Breuer. *Pflüger's Archiv*, 1891, Bd. xlviii, S. 195.
[32] *Idem.* *Sitzungsb. der Kais. Akad. der Wissensch.*, 1903, Bd. cxii, Abth. 3, S. 315.
[33] Bristowe. *Brain*, 1891, vol. xiv, p. 289.
[34] Broadbent, W. *Lancet*, 1897, vol. ii, p. 862.
[35] Brown, Crum. *Nature*, 1895, vol. lii, p. 185.
[36] Brown-Séquard. "Experimental Researches," New York, 1853, p. 18.
[37] Bruce, A. *Rev. of Neurol.*, 1903, vol. i, p. 329.
[38] Bruns, L. *Deutsche med. Wochenschr.*, 1892, S. 138.
[39] Cajal, S. R. "Travaux du Laboratoire de Recherches biologiques de l'université de Madrid," 1908, t. vi, p. 145.
[40] *Idem.* "Histologie du système nerveux," 1911, t. ii, p. 267.
[41] Clarke, R. H., and Horsley, V. *Brain*, 1905, vol. xxviii, p. 13.
[42] Collier and Buzzard. *Brain*, 1901, vol. xxiv, p. 198, Pl. XV, Tract Y.
[43] Curschmann. *Deutsche Arch. f. klin. med.*, 1874, Bd. xii, S. 356.
[44] Dejerine. "Anatomie des centres nerveux," Paris, 1901, ii, p. 405.
[45] Dejerine et Roussy, G. *Rev. neurol.*, 1905, t. xiii, p. 161.
[46] Deganello. *Riv. sper. di freniatr.*, 1899, vol. xxv, p. 1.
[47] Demoor. *Arch. de Zool. Exper.*, 1891, 2me sér., t. ix, p. 196.
[48] Economo, C. v. *Jahrb. f. Psychiat. u. Neurol.*, 1911, Bd. xxxii, S. 107.
[49] Edinger, E. "Vorlesungen über die Nervösen Centralorgane," Leipzig, 1904, S. 249.
[50] *Idem.* *Neurol. Centralbl.*, 1899, Bd. xviii, S. 95.
[51] Ewald, W. F. *Pflüger's Archiv*, 1907, Bd. cxvi, S. 188.
[52] *Idem.* *Arch. f. Psychiat.*, 1910, Bd. xlvii, S. 954.
[53] Fano, G. *Riv. sper. di freniatr.*, 1885, vol. xi, p. 480.
[54] Ferrier, D. *Proc. Roy. Soc.*, 1890, No. 286.
[55] Ferrier, D., and Turner, A. *Phil. Trans. Roy. Soc.*, 1894, B., vol. clxxxv, p. 719.
[56] Ferrier, D., and Yeo. *Phil. Trans. Roy. Soc.*, 1884, B., vol. clxxv, p. 561.
[57] Flourens, P. "Recherches expérimentales sur le système nerveux," 2me ed., Paris, 1842, p. 15.
[58] Foville. *Gaz. hebdom.*, 1859, t. vi, p. 146.
[59] Fraser, E. N. *Journ. of Physiol.*, 1901-02, vol. xxvii, p. 372.
[60] Friedberg. *Arch. d. Heilk.*, 1861, Bd. ii, S. 385.
[61] Fuse, G. *Arbeiten a. d. hirn. Anat. Inst. des Univer. Zürich.* 1912, Heft vi, S. 29.
[62] Gee and Tooth. *Brain*, 1898, vol. xxi, p. 15.
[63] Gehuchten, V. van. *Névraxe*, 1904, t. vi, p. 63.
[64] Goldstein, K., und Baumm, H. *Arch. f. Psychiat.*, 1913, Bd. lii, S. 373.

[65] Gowers, W. R. "Manual of Nervous Diseases," London, 1893, vol. ii, p, 185.
[66] Grasset. *Sem. méd.*, 1904, t. xxiv, p. 153.
[67] Graux. "Paralysie de l'oculomotion externe," *Thèse de Paris*, 1878, Obs. x.
[68] Held. *Arch. f. Anat. u. Physiol.*, 1893 (Anat. Abth.), S. 229.
[69] Högyes. *Pflüger's Archiv*, 1881, Bd. xxvi, S. 558.
[70] *Idem.* *Ungar. Akad. d. Wissensch.*, Mat. phys. Klasse, 1885, Bd. xi, No. 1.
[71] Holmes, G., and Stewart. *Brain*, 1905, vol. xxviii, p. 522.
[72] Hösel. *Monatsschr. f. Psychiat. u. Neurol.* 1899, Bd. vi, S. 168.
[73] *Idem.* *Arch. f. Psychiat.*, 1905, Bd. xxxix, S. 195.
[74] Hughlings Jackson. *Med. Times and Gaz.*, 1874, vol. i, p. 6.
[75] Hunnius. "Zur Symptomatologie der Brückenerkrankungen," Bonn, 1881, S. 15.
[76] Jelgersma, G. "Physiologie van het Cerebellum," 1904, Amsterdam Scheltema, Bl. xxiv.
[77] Kaplan und Finkelnburg. *Monatsschr. f. Psychiat.*, 1900, Bd. viii, S. 210.
[78] Karplus und Economo. *Arch. f. Psychiat.*, 1910, Bd. xlvi, S. 275.
[79] Knoll, Ph. *Sitzungsb. der Kais. Akad. der Wissensch.*, 1886, Bd. xciv, Abth. 3, S. 220.
[80] Kohnstamm, O., und Quensel, F. *Neurol. Centralbl.*, 1908, Bd. xxvii, S. 242.
[81] *Idem.* *Monatsschr. f. Psychiat. u. Neurol.*, 1900, Bd. viii, S. 261.
[82] *Idem.* *Journ. f. Psychol. u. Neurol.*, 1910, vol. xvi, p. 93.
[83] Kooyker, H. A. *Zeitschr. f. klin. Med.*, 1894, Bd. xxiv, S. 605.
[84] Kubo. *Pflüger's Archiv*, 1906, Bd. cxiv, S. 143; *ibid.*, 1906, Bd. cxv, S. 457.
[85] Landouzy, L. "Etude des Convulsions," *Thèse de Paris*, 1876, p. 20.
[86] Lange, J. de. *Fol. Neurobiol.*, 1909, vol. iii, p. 649.
[87] Lee, F. S. *Journ. of Physiol.*, 1894, vol. xvii, p. 192.
[88] Levinsohn. *Arch. f. Ophthal.*, 1909, Bd. lxxi, S. 313.
[89] Lewandowsky. "Leitungsbahnen des Truncus Cerebri," &c., Jena, 1904, p. 80.
[90] *Idem.* *Lehrb. f. Nervenkrankh.*, 1910, Bd. ii, S. 733.
[91] Lewy. *Fol. Neurobiol.*, 1909, vol. ii, p. 479.
[92] Lloyd. *Journ. of Physiol.*, 1899-1900, vol. xxv, p. 191.
[93] Loeb, J. *Pflüger's Archiv*, 1891, Bd. l, S. 66.
[94] Longet. "Anatomie und Physiologie des Zentralnervensystem," 1847, Bd. i, S. 355.
[95] Luciani, L. "Cerveletto," 1892,
[96] *Idem.* "Physiologie des Menschen," 1907, vol. iii, p. 454.
[97] Macgregor, A. *Lancet*, 1886, vol. ii, p. 1127.
[98] Magnus und de Kleijn. *Pflüger's Archiv*, 1912, Bd. cxlv, S. 467.
[99] Marburg. *Deutsche Zeitschr. f. Nervenheilk.*, 1911, Bd. xli, S. 41.
[100] Marina, A. *Deutsche Zeitschr. f. Nervenheilk.*, 1912, Bd. xliv, S. 138.
[101] Mingazzini. *Deutsche Zeitschr. f. Nervenheilk.*, 1901, Bd. xix, p. 1.
[102] Mingazzini und Polimenti. *Monatsschr. f. Psychiat. u. Neurol.*, 1906, Bd. xx, S. 403.
[103] Monakow, C. von. "Gehirnpathologie," "Nothnagel's Handbuch,' Wien, Bd. ix, T. i, S. 581.
[104] *Idem.* *Arch. f. Psychiat.*, 1895, Bd. xxvii (Beobachtung ii), S. 101.
[105] Mott, Schuster and Sherrington. *Proc. Roy. Soc.*, 1911, B, vol. lxxxiv, p. 67.
[106] Munk, H. *Sitzungsb. der Kais. Preusz. Akad. der Wissensch.*, 1906, S. 443.
[107] Muskens, L. J. J. *Journ. of Physiol.*, 1904, vol. xxxi, p. 204.
[108] *Idem.* *Trans. Roy. Acad. Amsterdam*, Communication, October 25, 1912, Bl. 656; *Nederl. Dierk. Vereen.*, Juli, 1913.
[109] *Idem.* *Trans. Roy. Acad. Amsterdam*, Communication, April 19, 1913, Bl. 1474.
[110] *Idem.* *Arch. f. Anat. u. Physiol.*, 1904 (Physiol. Abth.), S. 49.
[111] *Idem.* *Epilepsia*, 1912-13, Bd. iv, Fasc. 4, S. 429.
[112] *Idem.* *Psychiat. en Neurol. Bl.*, 1906, Bd. x, S. 68.
[113] *Idem.* *Verhandl. der Kon. Acad. Amsterdam*, 1902, Bd. viii, No. 5.
[114] *Idem.* *Trans. Roy. Acad. Amsterdam*, Communication, January 25, 1906.
[115] *Idem.* *Neuraxe*, 1913, vol. xiv, p. 299.
[116] *Idem.* "Report Zoological Station den Helder Staatscourant," 1894.
[117] *Idem.* *Psychiat. en Neurol. Bl.*, 1897, S. 328.
[118] Nagel, W. *Zeitschr. f. Psychol.*, 1896, vol. xii, S. 331.

[119] Oppenheim, H. *Arch. f. Psychiat.*, 1891, Bd. xxii, S. 27.

[120] Polimanti. *Zool. Jahrb.*, 1911, Bd. xxx (Zool. Abth.), S. 512.

[121] Prévost. "Cinquantenaire de la Societé de Biologie," 1899, p. 99.

[122] *Idem.* "Déviation conjugée," *Thèse de Paris*, 1868, p. 123.

[123] Probst, M. *Jahrb. f. Psychiat.*, 1901, Bd. xx, S. 41; *ibid.*, 1903, Bd. xxiii, S. 63.

[124] *Idem.* *Arch. f. Psychiat.*, 1900, Bd. xxxiii, S. 783; 1902, Bd. xxxv, S. 22.

[125] *Idem.* *Sitzungsb. der Kais. Akad. der Wissensch.*, 1905, Bd. cxiv, Abth. 3, S. 173.

[126] *Idem.* *Deutsche Zeitschr. f. Nervenheilk.*, 1898, Bd. xiii, S. 384.

[127] Prus, J. *Wien. klin. Wochenschr.*, 1898, Bd. xi, S. 857.

[128] Quensel, F. *Pflüger's Archiv*, 1911, Bd. cxxxix, S. 47.

[129] Quix. *Tijdschr. der Nederland. Dierk. Vereeniging*, 1903, p. 1.

[130] Redlich, E. *Monatsschr. f. Psychiat.*, 1899, Bd. v, S. 119.

[131] Rickards. *Brit. Med. Journ.*, 1886, vol. i, p. 774.

[132] Rothfeld, J. von. *Verhandl. deut. Naturforsch. und Aerzt.*, 1913, 85 Versamml., T. i, S. 269.

[133] *Idem.* *Pflüger's Archiv*, 1912, Bd. xlix, S. 440.

[134] Rothmann. *Neurolog. Centralbl.*, 1900, vol. xix, p. 44.

[135] Roussy, G. "Couche Optique," *Thèse de Paris*, 1907, pp. 175-177.

[136] Russell, R. *Phil. Trans. Roy. Soc.*, 1894, B., vol. clxxxv, p. 837.

[137] *Idem.* *Journ. of Physiol.*, 1894-95, vol. xvii, pp. 1 and 385.

[138] *Idem.* *Brit. Med. Journ.*, 1896, vol. ii, p. 914.

[139] Rynberk, van. "Cerebellum. Bataafsch Genootschap," 1906, Blz. ii, 35.

[140] Sachs, E. *Brain*, 1909, vol. xxxii, p. 180.

[141] Savill and Bennett. *Brain*, 1890, vol. xii, p. 102.

[142] Schäfer and Horsley. *Phil. Trans. Roy. Soc.*, 1888, vol. clxxix, pp. 29 and 32.

[143] Schiff, M. *Arch. de sci. phys. et natur.*, Geneva, 1891, 3me sér., t. xxv, p. 194.

[144] *Idem.* *Arch. f. physiol. Heilk.*, 1846, Bd. v, S. 667.

[145] Schwahn. "Beiträge zur Anatomie und Physiologie, v. Eckhard," Bd. viii, Heft iii, und Bd. ix, S. 193.

[146] Schwarz, E. *Monatsschr. f. Psychiat. u. Neurol.*, 1912, Bd. xxxii, S. 149 und S. 153.

[147] Sherrington, C. S. "The Integrative Nervous System," London, 1910, p. 55.

[148] Spiller, G. *Journ. of Nerv. and Ment. Dis.*, 1905, p. 569.

[149] Spitzer, A. *Obersteiner's Arbeiten a. d. Neurol. Inst.*, *Wien*, 1899, Heft vi, S. 38.

[150] Spitzer und Karplus, J. P. *Hidirn, ibid.*, 1907, Bd. xvi (T. ii), S. 348.

[151] Spitźka, G. *Neurolog. Centralbl.*, 1885, p. 246.

[152] Steel, J. J. "Diseases of Sheep," London, 1890, p. 338.

[153] Steiner. "Functionen des Centralnervensystem," Brunswick, 1886, p. 56.

[154] Thomas. *Rev. Neurol.*, 1903, vol. xi, p. 95.

[155] Topolanski, A. *Arch. f. Ophthal.*, 1898, Bd. xlvi, S. 452.

[156] Uexkull. *Zeitschr. f. Biol.*, 1895, Bd. xxxi, S. 593.

[157] Uhthoff. Graefe-Saemisch, "Handbuch der Augenheilkunde," 1911, Bd. xi, Abth. 2A, S. 1180.

[158] Valkenburg, C. v. *Proc. Roy. Acad. Amsterdam*, March 30, 1912.

[159] Vulpian. "Leçons sur la Physiologie du Système nerveux," Paris, 1866.

[160] *Idem.* *Gaz. méd. de Paris*, 1862, t. xxxii, p. 312.

[161] Wallenberg, W. *Deutsche Zeitschr. f. Nervenheilk.*, 1911, Bd. xli, S. 8.

[162] *Idem.* *Anat. Anzeig.*, 1900, Bd. xvii, S. 107.

[163] *Idem.* *Ibid.*, 1904, Bd. xxiv, S. 142.

[164] *Idem.* *Ibid.*, 1907, Bd. xxxi, S. 369.

[165] *Idem.* *Deutsche med. Wochenschr.*, 1910, Bd. xxxvi, S. 2229.

[166] Wernicke. *Arch. f. Psychiat.*, 1889, Bd. xx, S. 243.

[167] Wiersma, E. *Psychiat. en Neurol. Bladen*, 1899, Blz. 603.

[168] Winkler, C. *Trans. of Third Internat. Neurol. Psychiat. Congress of Amsterdam*, 1908, p. 132.

[169] *Idem.* "Nervus Octavus," *Verhandl. der Kon. Acad. Amsterdam*, 1907, second section, vol. xiv, p. 26.

AN EXPERIMENTAL RESEARCH INTO THE ANATOMY AND PHYSIOLOGY OF THE CORPUS STRIATUM.[1]

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EXPLANATION OF LETTERING OF FIGURES.

AC	commissura anterior.
Al	ansa lenticularis.
ANR	anterior capsule of nucleus ruber.
CE	capsula externa.
CGE	corpus geniculatum externum.
CI	capsula interna.
CIP	posterior part of capsula interna.
CL	corpus subthalamicum (Luysii).
CR	crus.
Figp	internuncial fibres of globus pallidus.
Fip	internuncial fibres of putamen.
Fl	Forel's lenticular bundle (H_2).

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FlNR	ansa lenticularis fasciculi, via Forel's field, to nucleus ruber.
Fsl	strio-luysian fibres.
Fth	Forel's thalamic bundle (H_1).
GP	globus pallidus.
L	lesion.
Lam_1	lamina medullaris lateralis.
Ln	locus niger.
M	fasciculus retroflexus of Meynert.
N II	nervus opticus.
N III	nervus oculomotorius.
NAm	nucleus amygdalæ.
NC	nucleus caudatus.
NFl	nucleus of Forel's field.
NR	nucleus ruber.
OT	thalamus opticus.
PCS	pedunculus cerebelli superior.
PUT	putamen.
V III	ventriculus tertius.
ZI	zona incerta.

INTRODUCTION.

The exact nature and function of the large mass of basal grey matter known as the corpus striatum have hitherto constituted, it is no exaggeration to say, one of the unsolved problems of neurology. Not that the corpus striatum has failed to attract the attention of anatomist, physiologist and clinician; on the contrary, since the days of Willis, it has received its full share of investigation along all the familiar lines. The disturbing element in the matter of research into its functions has been the conflicting nature of the results obtained. Anyone who will take the trouble to read the curiously philosophic text-books of half a century ago would imagine, it is true, that the corpus striatum was an organ as high in the cerebral hierarchy as the cortex itself, endowed with motor functions as elaborate and as detailed. But a change took place when neurologists realized that many of the functions assigned to it were the property of the adjacent cortico-spinal paths, and almost at once it seemed to fall from its high estate and depreciate in physiological significance. Under these circumstances the question of its function became an enigma, and, as a consequence, there was eventually assigned to it a varied assortment of motor, sensory, vasomotor, psychical and reflex functions, no one of which, it is safe to say, has ever rested on unequivocal evidence. To prove the truth of this statement it is only necessary to quote from such acknowledged authorities as v. Monakow, v. Bechterew and Edinger. In 1905 v. Monakow [56] wrote: "Trotzdem seit Jahren zahlreiche Forscher

bemüht sind, die klinischen Folgen von Läsionen im Gebiet des Streifenhügels und des Linsenkerns zu erforschen, und obwohl die Zahl von genaueren Beobachtungen über Herde in jenen Hirnteilen eine ganz stattliche ist (gehören doch Herde verschiedener Natur und Ausdehnung im Vorderhirnganglion zu sehr gewöhnlichen Vorkommnissen), so sind wir heute ebensowenig wie vor 25 Jahren Nothnagel imstande, sichere Kennzeichen einer Herderkrankung in den genannten Hirnteilen aufzustellen." In 1909 v. Bechterew [6] was compelled to say: "Die funktionellen Zustände des Schweifkerns und des Linsenkerns, welche seit jeher unter dem Gesamtnamen Corpus striatum zusammengefasst werden, sind gegenwärtig einer endgültigen Aufhellung noch immer nicht erschlossen. Über die Bedeutung dieser Gebilde gehen die Meinungen der Autoren, welche sich darüber geäussert haben, vielmehr noch sehr weit auseinander." No longer ago than 1911, Edinger [21] wrote: "Es gibt kaum einen Punkt, der so sehr beweist wie weit bisher noch unsere Beobachtungsfähigkeit zurück ist, als der Umstand dass wir bis heute weder von den Funktionen des Corpus striatum noch von den Symptomen etwas wissen, die eintreten, wenn es zerstört oder wenn es gereizt wird. Da ist ein mächtiger Hirnteil, der von enormer Bedeutung sein muss, sonst wäre er nicht von den Fischen an aufwärts vorhanden, ein Hirnteil der bei den Vögeln die Hauptmasse des ganzen Grosshirnes ausmacht, zudem ein Gebilde, in dem ausserordentlich oft beim Menschen Krankheitsherde gefunden werden und doch hat niemals jemand ein Symptom entdeckt, das von ihm ausgeht."

Within the last two or three years, however, the clinico-pathological method, to which we owe some of the greatest discoveries in neurology, has furnished evidence which goes far towards clearing away the obscurity that has surrounded the subject, and at the same time it has enabled us to reach a truer interpretation of the data obtained by experimental research on the corpus striatum, while it has also indicated the lines along which further experimentation must be prosecuted. As has so often happened before, once insight is gained into the function of a nervous organ, much that has hitherto seemed inexplicable becomes plain, and with notable rapidity further data are collected which bear out the new view. Already, in the last year or two, a syndrome of the corpus striatum has been enunciated which, however much it may come to be modified, shows every sign of being corroborated by each accession of fresh evidence, and in any case can fairly be regarded as furnishing the closest approximation to the exact mode of working of that important structure which has up to the present been reached.

Chapter I.—Historical.

The vicissitudes through which the corpus striatum has passed constitute an interesting chapter in cerebral physiology, affording an excellent illustration of the methods of procedure of early experimenters, and throwing a valuable sidelight on the stages whereby our present knowledge of the working of the encephalon has been attained.

In 1667, Thomas Willis described the corpora striata as "internodes by which the cerebrum coheres with the medulla oblongata," and on account of their peculiar structure attached such importance to them as to consider them the seat of the "sensorium commune." From this position of high significance thus assigned them by the earliest investigators—an inevitable consequence when we remember their prominent appearance on horizontal section—they have never really declined.

In 1740, Swedenborg [74], published his "Œconomia Regni Animalis," a book in which he showed curious insight into cerebral physiology. To the corpus striatum he attached much importance. Thus he says: "The royal road of the sensations of the body to the soul is through the corpora striata, and all determinations of the will also descend by that road." That organ is "the Mercury of the Olympus, it announces to the soul what is happening to the body, and it bears the mandate of the soul to the body." If we translate his somewhat figurative language into present-day terminology, it is clear that Swedenborg had a conception of afferent and efferent paths far in advance of his time, even though it be but the result of a lucky guess on his part, and that if we suppose he included the optic thalamus in the corpora striata, which lie immediately under and "are most immediately subject to the courts of the anterior (superior) regions of the cerebrum," he thereby developed a theory of the function of the basal ganglia in relation to the cortex which has been almost universally held and even yet is not without its bearing on the problem before us.

At the beginning of last century Burdach [12] (1819) showed that the outer aspect of the lenticular nucleus was unconnected with the fibres of the external capsule and held that the appearances suggested that the fibres of that nucleus did not go to the cortex. He concluded that the basal ganglia are in a psychical sense intermediate between the brain-stem and the cortex, controlling the one and being subsidiary to the other.

Apparently the earliest definite experiments on the corpus striatum were those conducted about the year 1820, by Flourens [26], who failed to obtain any movements in the rabbit by stimulation of the ganglion. "Je piquai d'abord, dans tous les sens, et j'enlevai ensuite en totalité, par tranches successives, sur un lapin, les corps striés et les couches optiques: nulle agitation n'accompagna cette double épreuve." He failed also, somewhat curiously, to obtain any movements by stimulation of the cortex, and declared that "les hemisphères cérébraux ne sont point susceptibles d'exciter immédiatement des contractions musculaires."

Magendie [49], however (1841), obtained diametrically opposed results. By mechanical stimulation of the nucleus caudatus with a needle he was unable to elicit movement. "Voici le ventricule latéral droit ouvert, la voûte et le septum lucidum enlevés: le corps strié paraît au fond de la plaie. Je pique ce corps avec une aiguille enfoncée d'arrière en avant: l'animal conserve toute son impassibilité. C'est en vain que je transperce le corps strié du côté gauche: les résultats sont toujours négatifs." By destroying the corpus striatum on both sides, however, the same experimenter obtained leaping forward of the animal as by an irresistible impulse. It should be stated that the majority of his experiments were on rabbits. "Ainsi, par exemple, je vais couper et extraire les corps striés: vous allez voir l'animal courir en avant comme emporté par une impulsion irrésistible. Il vient en effet de partir comme un trait: je suis obligé de le retenir, et vous voyez qu'il conserve l'attitude de la fuite." And again: "Je viens d'extraire un des deux corps striés: rien encore de modifié dans les mouvements. J'enlève le second corps strié: voyez comme l'animal cherche à fuir. Je ne veux pas le laisser libre, car il irait se briser la tête contre le premier obstacle qui se trouvait sur son passage."

Magendie was of the opinion that movements in a forward direction were under the influence of the cerebellum, while backward movements were controlled by the corpus striatum: if, therefore, the latter were destroyed, the animal should run forward, owing to uncontrolled action of the cerebellum. It is certain from the technique of Magendie that the white matter adjoining the corpus striatum was implicated in the experimental lesions, and their value is thereby discounted.

Longet [45] (1842) dismissed the theory held by Willis as one without any foundation, but admitted his inability to advance another more plausible. He experimented on rabbits, removing first the cerebral hemispheres and then the corpora striata, but failed to obtain Magendie's results, and concluded that "la force motrice spéciale que M. Magendie place dans les corps striés est une force purement imaginaire." He found that these structures were quite inexcitable. "Chez les animaux vivants les corps striés semblent être complètement insensibles aux irritants mécaniques : ils peuvent être dilacérés sans qu'il y ait manifestation d'aucun signe de douleur, sans que la moindre contraction musculaire survienne. Les fonctions spéciales des corps striés restent encore à démontrer."

Meanwhile Julius Budge [11] (1840) was obtaining still other results by the somewhat crude methods we have been considering. "I opened the skull of a young dog who had just been killed, and in a few minutes completely exposed the whole brain. At the same time my assistant had opened the abdominal cavity and laid out the intestines. I cut away the cerebral hemispheres, raised up the corpus callosum, and irritated with a sharp needle the optic thalami, corpora quadrigemina, and corpora striata, one after the other. The stimulating of the corpora striata and quadrigemina increased the motions of the intestines every time. When the peristaltic motion had completely ceased, I could reproduce it by again stimulating these organs. . . . This continued to be the case for scarcely five minutes, and then the irritability was entirely destroyed." "Thus it is proved that the nervous principle of the motion of the intestinal canal is seated in the brain : nay, the spot is accurately determined from which it proceeds, or rather, in which the nerves of the canal are concentrated. The central organ of the motion of the stomach was also shown in my experiments : it is in the right corpus striatum."

Magendie's views received some support from subsequent investigators, among whom may be mentioned Schiff [69], Beaunis [4], Fournié [28], Lussana and Lemoigne [47], and Nothnagel [59]. Fournié made injections of chloride of zinc into the caudate nucleus (dogs), obtained strong progression movements, and concluded that in the corpus striatum were excitable centres sending nerve-impulses peripheralwards for the carrying out of voluntary movements. Beaunis employed injections of caustic soda, liquor ferri sesquichlorati, and ammonia carmine, and also obtained forced movements (rabbits), but the crudity of these experimental methods is sufficiently obvious.

Nothnagel employed a fine needle, or rather syringe, wherewith to inject minute quantities of pure chromic acid into the caudate. At a particular spot in that ganglion, dignified by him with the name of the "nodus cursorius," stimulation of this sort always produced violent forward movements in the rabbits on which he experimented. If we read the original description, however, we note that it was only after an interval of from *two to ten minutes* that the animal "schliesslich in ein wildes Umherstürzen zum Teil mit Manègebewegungen und öfteren Anprallen an Wande, u.s.w., überging." The localizing value of the results is clearly infinitesimal. By stimulation of the lenticular nucleus after a similar fashion, especially in its anterior and middle parts, he obtained bending of the trunk with the concavity to the side of the lesion. He therefore endeavoured to distinguish between the caudate and the lenticular nuclei, placing in the former a centre for combined movements conditioned by psychical stimuli, and in the latter a centre for individual movements.

It might be supposed that the era of inexact experimentation would have passed whenever the method of electrical stimulation came into vogue. Such, however, at first, was far from being the case. In 1870 Hitzig [37] stimulated the lenticular nucleus by a special instrument ("Lanzenrheophor") through the frontal fissure, and obtained powerful contractions of the contralateral muscles, but the possibility of simultaneous cortico-spinal stimulation cannot be negatived. In 1874 Burdon Sanderson [68] adopted the simple expedient of dropping a needle vertically from the surface of the cortex and found it reached the corpus striatum in its posterior part at a depth of some 10 or 12 mm. Obtaining movements by stimulation at this point (cats), he concluded as follows: "From these facts it appears that the superficial convolutions do not contain organs which are essential to the production of the combinations of muscular movements now in question. They further make it probable that the doctrines hitherto accepted by physiologists, that the centres for such movements are to be found in the masses of grey matter which are to be found in the floor and outer wall of each lateral ventricle, are true."

It was in 1876 that Ferrier [23] published his well-known book, "The Functions of the Brain," which contains much of interest for our subject, and enables us to appreciate the way in which the corpus striatum was at that time generally regarded. One or two quotations may be given.

"The results of (electrical) stimulation of the corpora striata in monkeys, cats, dogs, jackals and rabbits are so uniform as to admit of being generalized together.

"Irritation of the corpus striatum causes general muscular contraction on the opposite side of the body. The head and body are strongly flexed to the opposite side, so that the head and tail become approximated, the facial muscles being in a state of tonic contraction, and the limbs maintained in a flexed condition. Apparently the individual movements excited from the various regions of the hemisphere are all thrown into action simultaneously, the flexors predominating over the extensor muscles."

The same author, it may be remarked, makes the express statement that "individual or differentiated movements are not capable of being excited by application of the electrodes directly to the corpus striatum." The general conclusion come to is that "in the corpus striatum there would thus appear to be an integration of the various centres which are differentiated in the cortex." The same view is expressed again in other sections of the book. Thus: "The motor combinations which are integrated in the corpus striatum are again differentiated in the cerebral hemispheres."

Now, up to this epoch clinicians generally had been fully convinced that the corpus striatum was a motor organ, and differentiation between disease of that ganglion and disease of the pyramidal paths was not attempted. In fact the anatomical conceptions holding sway at that time were all for regarding the corpus striatum as an actual station on the path between cortex and cord. In 1866, for instance, Broadbent [10] said that "to the motor nuclei of the cord fibres descend in the antero-lateral white columns from the corpus striatum, decussating at the point of the medulla." It is hardly necessary to point out that this view assumes that the pyramidal paths issue directly from the corpus striatum. The same assumption is tacitly made in all the writings of the period, and occurs again and again in records of hemiplegic and other cases.

Although apparently attached to this opinion, Ferrier endeavoured to separate the function of the cortex from that of the basal ganglia. He states that "the various physiological and pathological data which have been advanced to show that destruction of the corpus striatum causes paralysis of voluntary motion . . . do not suffice to determine the special function of these ganglia as distinct from the cortical centres." He puts the problem very clearly when he says that "we . . . have to ascertain whether any special differences are observable between the symptoms resulting from lesions of the cortical centres and those following lesions of the basal ganglia, which may indicate what special functions these ganglia, as such, subserve."

After pointing out how greatly animals differ in respect to the degree of independent organization of motor activities in centres below the cortex (to which important consideration attention will subsequently be devoted), the same experimenter concludes from the facts of comparative physiology that the corpora striata are centres in which habitual or automatic movements become organized. With the proviso that in man even the most habitual or most automatic actions require the co-operation of the centres of conscious activity, he holds that by virtue of a short circuit from afferent to efferent side, from the optic thalami to the corpora striata, movements in response to immediate sensory impressions take place, and that there is every reason to believe the basal ganglia suffice to a large extent for the execution of habitual movements.

These early views of Ferrier were based upon the assumption to which reference has already been made, that the peduncular or cortico-spinal fibres and the ganglionic substance of the corpus striatum formed a complex whole. The corpora striata were held by him to be the ganglia of interruption of the projection system of the foot or basis of the crus, "an anatomical indication of their motor signification." The integral connexion of the pyramidal path and the corpus striatum he regarded as established, and in view of our present-day knowledge it is historically interesting to note that at that date there was greater diversity of opinion in regard to the significance of the optic thalamus, the facts of pathology as far as the corpus striatum was concerned being supposed to be constant and uniform.

The theory that the actions which are regarded as inherited instincts, all the compound reflex, automatic, habitual actions of man, which had, through long-continued repetition, assumed the character of acquired instincts, were co-ordinated or integrated in the basal ganglia, seemed for a long time to satisfy the neurologist. It is odd to note, however, how carefully the writers of that time avoid declaring that automatic movements are actually *localized* in the corpus striatum. Ross [66], for instance, says that "all complex movements which animals manifest in response to emotional disturbances are *organized* in the corpus striatum." Speaking of a cat "spitting," he remarks: "The regulation of the movements concerned is *organized* in the corpus striatum, but the incitement to the action of these centres comes from the cortex." (Italics my own.) It is a little difficult clearly to follow this distinction, and Ross himself elsewhere hinted he had begun to doubt the subordination of the corpus striatum to the cortical motor centres. In fact, he says in another place: "The corpus striatum must be regarded as a nerve centre co-ordinate with, and not subordinate to, the cortex."

François-Franck and Pitres [29] (1878) exposed the corpus striatum in dogs by removing the cortex. They obtained no movements from localized electrical stimulation of the caudate and lenticular nuclei: whenever the electrodes were applied to the internal capsule, there was a marked response. They found a striking contrast between the results of feeble stimuli applied to the internal capsule and strong stimuli applied to the corpus striatum. They considered the corpus striatum definitely inexcitable.

Already, however, Flechsig [24], and later Wernicke [79], and Charcot [14], were coming to the conclusion that the great majority of the fibres of the pyramidal system are uninterrupted on their way from cortex to crus through the basal ganglia and that the corpus striatum is a ganglion independent of the cortex, possessing no cortical projection - system. Whenever it was demonstrated that hemiplegia and hemianæsthesia were caused by injury to the fibres between the basal ganglia and not by lesions of the ganglia themselves, the importance of the corpus striatum forthwith diminished, and once again its nature and functions became shrouded in obscurity. For a long time no work was done on the subject. Attention was directed rather to a study of the functions of the cortico-spinal system. Cases began to accumulate where lesions of the corpus striatum were unaccompanied by recognizable symptoms during life. The view was expressed that lesions of the lenticular nucleus, for instance, were always silent.

Since that time, opinion has been divided on the motor function of the corpus striatum. Its excitability has been as much denied as accepted. Luciani and Tamburini [46] considered that under given pathological conditions the caudate nucleus could take on the functions of the motor cortex (dogs, apes, rabbits). Lo Monaco and Bellanova [44] destroyed the nucleus caudatus in dogs, but, obtaining results more or less similar to those from lesions of the cortex, regarded the corpus striatum as an included portion of the motor cortex, and considered it closely connected with the latter. Bianchi [7] stimulated the corpus striatum with platinum needle electrodes in dogs and rabbits, and, obtaining in certain cases pleurosthotonus with movements of the head and extremities, held to the opinion of Hitzig, that the corpus striatum was electrically excitable.

Baginsky and Lehmann [3] (1886) considered the nucleus caudatus an integral part of the motor region of the brain (rabbits, cats).

From his experimental investigations Munk [58] (1884) came to the conclusion that the structure in question was concerned with habitual movements.

Johansen [39] (1885), experimenting on dogs, obtained tonic cramps from stimulation of the lenticular nucleus, and concluded that that organ was concerned with the genesis of convulsions. In fact, he held that epileptiform seizures in man, unaccompanied with loss of consciousness, arose in the lenticular nucleus.

But other investigators, among whom may be mentioned Gliky [32] and Braun [8], obtained entirely negative results.

In 1889 [54] Minor performed a series of carefully planned experiments on rabbits, dogs, cats, and guinea-pigs. He showed clearly that the movements apparently elicited from stimulation of the caudate were due to overflow of the current to the neighbouring capsule. He repeated Nothnagel's experiments and demonstrated that the results came from the capsule, and in order to establish this beyond cavil he performed the crucial experiment of previously causing the whole pyramidal system to degenerate by removing the motor cortex. Thereafter he failed, even with strong currents, to obtain movements from the corpus striatum. The motor function of that organ, therefore, became more than ever doubtful.

In 1890, Ziehen [83] reached a similar conclusion (rabbits). He showed that not a few of the movements hitherto supposed to come from stimulation of the caudate in reality came from the genu of the capsule. He noticed that the nearer the stimulating needles were to the capsule, the more certain were the motor phenomena that resulted. When electrodes were pushed into the mass of the corpus striatum tonic convulsions followed after some thirty seconds, a condition which, in his opinion, could only be regarded as a capsular effect. With removal of the whole motor region, faradic stimulation of the lenticular nucleus was always negative.

Prus [65] (1899) in his experiments pushed the sinus longitudinalis aside, cut through the corpus callosum, and opened the lateral ventricles, exposing the ventricular surface of the caudate. He obtained tonic cramps in the contralateral limbs from stimulation of the posterior part of the caudate, clonic cramps from the middle, and running movements from the anterior section. In addition, he noted inhibition of respiration from stimulation of the middle division of the caudate, with elevation of blood-pressure and slowing of the pulse-rate. He concluded that some of his results were the expression of reflexes aroused by stimulation of afferent or sensory nerves, but that the tonic and clonic twitchings, and the rise of blood-pressure, were the direct result of electrical irritation. Prus supposed that the caudate played a part in voluntary movement and in automatic movements, such as running or walking, and that it contained a vasomotor and vasoconstrictor centre.

Wieting [81] (1891) and Wertheimer and Lepage [80] (1897) found the corpus striatum inexcitable (dogs).

Probst (1901) destroyed the nucleus caudatus, leaving the capsule intact, and could not obtain any paralytic or even paretic phenomena.

In 1902, Schüller [70] repeated and revised these experimental methods, and once more the result was negative (dogs). The caudate, and corpus striatum generally, he always found inexcitable from an electrical standpoint. Schüller also observed quickening of respiration from stimulation of the caudate, especially in its anterior part, but no respiratory effect could be elicited when the capsule was allowed to degenerate. As, however, the acceleration of respiratory rhythm was more readily obtained from the caudate than from the capsule, he concluded that, possibly, there was a local connexion between the former and the capsular fibres concerned with respiration, which, in his view, were probably part of the cortico-thalamic system, passing to the median nucleus of the thalamus.

Stieda [73] (1903), after preliminary degeneration of the whole cortico-spinal system, directly stimulated the caudate in dogs, but obtained no movements whatever.

At various times during the last twenty years, v. Bechterew [6], in collaboration with one or other of his pupils, has performed experiments on the corpus striatum which have been collected and published in the second volume of "Die Funktionen der Nervencentra" (1909).

Von Bechterew's first series of experiments (dogs) were undertaken in 1886. After previously effecting complete degeneration of the pyramidal tract by extirpation of the motor area he was unable to obtain any motor phenomenon by strong stimulation of the caudate nucleus. Again, with Stieda, in 1902, similar researches were undertaken, but in every instance the result was negative. Von Bechterew concludes that it must be considered beyond dispute that the caudate nucleus has nothing to do with automatic movements, still less with volitional movements.

On the other hand, however, he reached a somewhat different conclusion with regard to the lenticular nucleus. With Schaikewitsch, in 1902, he experimented on dogs, either removing the hemisphere so as to stimulate the lenticular nucleus directly, or previously destroying the pyramidal system and then pushing an electrode for a given depth into the nucleus through the sylvian fissure. In the majority of his experiments he obtained tonic contractions of the opposite limbs, and of the head and tail, and also generalized epileptiform convulsions on both sides of the body. He obtained these phenomena even when the pyramidal path was degenerated by preliminary extirpation of the motor cortex. Von Bechterew concludes that the lenticular nucleus has a motor function: that in the globus pallidus is a special tract of extra-pyramidal fibres stimulation of which effects movements on the opposite side of the body. The putamen he associates with the caudate nucleus, presumably denying to it any function of a like nature.

Grünstein [35] (1911) made lesions in the caudate and lenticular nuclei in dogs and rabbits with a specially constructed needle, but as his paper contains no mention of physiological results, and is concerned solely with the anatomy of the corpus striatum, it need not be further alluded to at present; due reference will be made to his anatomical findings in subsequent chapters.

In the review of the experimental literature on the corpus striatum that has been given, reference has been made more than once to a possible association of these masses of grey matter with the functions of the viscera, and some evidence has accumulated which goes to show that there may be connexions between the corpus striatum and the functions of respiration, circulation, and the maintenance of body temperature, as well as possibly the function of the bladder and alimentary tract. As my own experimental researches have been concerned with the motor part of the subject, this question may be left to one side for the present.

CHAPTER II.—PERSONAL EXPERIMENTAL RESEARCHES.

The research was carried out in the laboratory of experimental neurology at University College, under the ægis of Sir Victor Horsley, who performed my operations for me, and to whom I am very greatly indebted for much generous help and advice.

Methods.

Some twenty-five monkeys were experimented on (*Macacus rhesus*, *Macacus sinicus*). Both stimulation and electrolytic methods were utilized. The instrument employed was the stereotaxic instrument of Clarke and Horsley [38], which is fully described in BRAIN, vol. xxxi, p. 45. It may be said here, very briefly, that its purpose is to direct a needle in any one of three planes. The average size of rhesus heads varying very slightly within certain limits, a brass cage is devised, inside which the animal's head is fixed. The vertico-transverse plane which passes through the external auditory meatus on either side, known as the interaural plane, is taken as zero. On the brain of the rhesus it passes almost constantly just behind the upper limit of the fissure of Rolando. A horizontal plane passing through the inferior margin of the bony orbits and the external auditory meatus, known as the basal plane, is taken as zero for up and down measurements. By means of a series of photographs of vertico-transverse sections of a frozen rhesus head with the brain in situ, cut 2 mm. thick and numbered from the interaural plane forwards, it has been possible to decide with the greatest accuracy at what point to stimulate, or to electrolyze. Thus: a plane about 12 mm. in front of the interaural plane cuts through the three segments of the lenticular nucleus. The needle carrier is accordingly moved the requisite distance along a measured antero-posterior brass bar, which brings the point of the needle opposite this desired plane. Then the depth from the surface of the spot to be stimulated is measured on the photograph corresponding to the plane (to all the photographs a millimetre scale is appended) and found to be, say, 16 mm. The needle-point is therefore moved inwards 16 mm. from the surface of the cortex along the needle carrier, and we know for a certainty, if the carrier is at the correct height above the basal plane, that the point of the needle is somewhere in the globus pallidus. The precision of the instrument is admirable, and results were obtained from the very first.

The needle consists of a fine-drawn double capillary glass tube, inside which, insulated by the glass, are two fine platinum wires. At the end of the needle they are naked for the extent of less than half a millimetre, and when the other ends are connected up to a battery and a constant current allowed to flow, a limited electrolytic lesion is readily produced. In the series of experiments most of the lesions were made with a current of 3 to 5 ma. running for 5 to 15 minutes. The damage made by the passage of the needle through the cerebral tissues is astonishingly slight, and easily distinguishable afterwards from the main lesion.

It does not take long before one learns where the projection of the corpus striatum on the lateral aspect of the cerebral hemisphere is to be traced. If the point of the needle be introduced through the operculum, through the lower extremity of the third frontal gyrus, through the upper or middle part of the superior temporal gyrus, it is certain to strike the lenticular nucleus at a depth of 12 to 16 mm. on vertico-transverse planes some 9 to 13 mm. in front of the interaural plane, which, as already mentioned, passes just behind the upper limit of the fissure of Rolando.

Stimulation Experiments.

In the great majority of the macaque monkeys experimented on it was made a routine practice to stimulate the lenticular nucleus electrically before proceeding to make electrolytic lesions. The procedure was as follows: The animals were always under deep anæsthesia induced by chloroform and continued with ether. By the help of the photographs of the normal macaque head, already referred to, it was a simple matter to determine the position of the point of the stimulating needle. A plane 10 mm. in front of the interaural zero plane was commonly chosen to commence with. In the vertical direction a plane about 12 or 13 mm. above zero usually brought the needle opposite the lower part of the gyrus overhanging the sylvian fissure; 10 mm. above zero was opposite the upper part of the superior temporal gyrus; 5 or 6 mm. above zero was opposite the middle part of the same gyrus. In this plane 10 mm. in front of the interaural zero, and on the 10 mm. plane above the base line, it was very commonly found that when the needle was driven into the brain for a distance of 10 mm. its point was on or just internal to the external capsule. By working forwards and backwards from the 10 mm. frontal plane, 2 mm. at a time, by carrying the needle upwards and downwards in each plane, and by advancing the needle-point 2 mm. at a time from the external capsule inwards to the internal capsule, it has been possible to stimulate systematically the whole of the lenticular nucleus in all its segments. Further, at any given point, it was made a frequent practice to commence with the secondary of a Kronecker coil at 500 on the scale, or even less, and to advance it to 1,000, 2,000, 5,000 or even 10,000 on occasion, without altering the needle position; in this way the results of current spread were easy of detection. A double needle was nearly always the one employed; in this way bipolar excitation was applied to very small areas. The current utilized was the faradic, derived from the coil above mentioned. Every gradation from feeble currents upward was readily and conveniently obtainable.

From what has been said it will be understood that the control over the position of the needle-point is complete, and that the operator is able to say at any given moment exactly what part of the lenticular nucleus is being stimulated. So far from desiring to exclude pyramidal or cortico-spinal paths by previous section and subsequent degeneration, it was rather an advantage to have their integrity unimpaired, as the contrast between stimulation of the nucleus and of the capsular fibres was rendered so striking thereby as by itself to constitute satisfactory proof of the difference in electrical excitability between the two.

It may be said at once that the lenticular nucleus was found to be electrically inexcitable. In the first place, with the needle in the centre of the putamen, even comparatively strong currents failed to produce any discoverable motor phenomenon in any muscular group. This was noted again and again. The same is true also of the globus pallidus. An identical current, employed by way of control, was found to produce movements at once from the motor cortex. Whenever the immediate neighbourhood of the internal capsule was reached typical movements were obtainable, and with the needle in the capsule, of course, often powerful movements were elicited. It was frequently observed that with weak currents, advancing the needle-point merely 2 mm. made all the difference between no movement and a capsular movement, showing the genuine inexcitability of all but the corticospinal fibres. It may be definitely stated, as a result of the researches here described, that investigation of the whole of the lenticular nucleus with a stimulating needle has failed to elicit any evidence in the ape of the localization of motor centres there, comparable to the centres of the excitable motor cortex.

In the second place it occasionally happened that certain movements occurred while the nucleus was being explored with the needle, but these were always variable, inconstant, and fleeting. First of all it was sometimes found that homolateral movements of the face, mouth, or tongue took place from stimulation towards the outer surface of the putamen and the external capsule. These were neither strong nor persistent, and in any case they were far from constant. The mechanism of their production is interesting, but is outside the purpose of the present communication. Next, it was occasionally noted that blinking movements of both eyes occurred; the animal sometimes opened its eyes and stared straight in front, sometimes one or other or both eyes blinked; very occasionally the eyes rolled indefinitely and then came into a fixed midway position; sometimes the mouth opened slightly and symmetrically. It was impossible to obtain these movements with any regularity; oftener than not they were conspicuous by their absence. It cannot be said that the occurrence of such movements, obtained for that matter in the stimulation of quite other areas and dependent to some extent on the degree of anæsthesia, is any indication of their being localized in the nucleus lentiformis. My experiments have uniformly failed to demonstrate the occurrence of tonic contractions of the opposite limbs, and epileptiform convulsions, such as v. Bechterew [6] says he obtained from stimulation of the lenticular nucleus. The fact must not be lost sight of that the animals he experimented on were dogs, whereas my experiments were on monkeys.

Again, it was observed occasionally that a particular movement, say slight closure of the contralateral hand, was produced by stimulation with the needle-point close to the capsule, judged by its distance in from the surface, and that stimulation with the needle advanced a further 2 mm. produced the same movement much more powerfully and unmistakeably; under such circumstances there can be no doubt that in the first instance the movement was not truly lenticular in origin but resulted merely from the propinquity of the needle-point to capsular fibres and from spread of current.

Thus from a consideration of the above-mentioned data it is clear that when due precautions are taken, when exact control both of current and of position of needle is possible and is practised, stimulation of the lenticular nucleus, both putamen and globus pallidus, is essentially negative. In this respect my research but confirms the work of those previous investigators who have performed their experiments in a sufficiently careful and accurate fashion.

Electrolytic Lesions.

(*A*) *Physiological results.*—It has already been stated that for the production of electrolytic lesions a constant current of from three to five or more milliampères was utilized, and allowed to run for some five to fifteen minutes. Both small and large lesions were made, the latter by making two, three, or four smaller lesions close together. While in some instances the lesions were intentionally placed, for anatomical reasons, in the vicinity of, but outside the nucleus lentiformis, reference will now be made solely to those in which they were situated entirely within the nucleus.

The animals were allowed to live as a rule for some three weeks after the operation. In practically every instance uninterrupted recovery took place. During these weeks the animals were tested in all sorts of ways: they were allowed to climb about the room used as a monkey-house, they were tried with the use they made of objects in either hand, their reflexes were examined, &c.

For reasons which will be mentioned subsequently, in the first monkeys experimented on the lesions were single and small. None of these animals showed any sign of motor impairment that careful and repeated examination could detect. No involuntary movements, *e.g.*, of the nature of tremor, were noticed. In the later series of experiments, where the lesions were larger, involving the greater part of the nucleus, the absence of any involuntary movement was again noted. Some of these monkeys, however, showed a preference, in the taking of nuts or bananas, for the homolateral limb. Or, in climbing about their cage, they showed just the least awkwardness or clumsiness with the contralateral limbs. Yet no approximation to paralysis or even paresis was seen. It was impossible to satisfy oneself that there was any undeniable alteration in the tone of the muscles of the limbs opposite to the lesion. In several instances the tendon reflexes were slightly increased in the contralateral limbs. There was no defect of sensibility as far as could be ascertained.

In one or two cases it is possible that slight implication of some capsular fibres may account for the motor symptoms, such as they are; in others, however, microscopical examination failed to demonstrate capsular degeneration, and yet the animal's limbs on the side opposite to the lesion were not perfectly normal. It is therefore conceivable that a large lenticular lesion produces an unsteadying effect in innervation. But the data at my disposal preclude any elaboration of this. All that can be said is that small and large lesions alike failed to reveal themselves by any obvious or constant or unequivocal defect of motility, as far as the results of the present investigation are concerned. In this series, as a matter of fact, no bilateral lesions were made.

The opportunity was taken, in a number of cases, of stimulating the homolateral motor cortex after large lesions in the lenticular nucleus. The result in every instance was the same; no difference in excitability could be detected between corresponding points on the right and left motor cortical areas. These excitation experiments were made after the full three weeks, *i.e.*, after degeneration secondary to the lesion was thoroughly established. Thus there is no physiological evidence of impairment of function of the motor area from large lesions in the homolateral corpus striatum.

(*B*) *Anatomical results.*—As already stated, the animals operated on under strict antiseptic precautions were allowed to live about three weeks; they were then killed under an anæsthetic. The brain was at once injected in situ with formol-Müller, removed, and the position of the interaural plane marked on it. A few days later it was cut in 2 mm. slabs, parallel to the interaural plane, by means of Clarke's macrotome. The slabs showing the lesions were then photographed, and the material duly prepared for examination by Marchi's method.

In the following pages a selection only from the complete set of investigations will be given. It will be understood that a description of each would result in much overlapping, and also that in some animals the results were scantier or less instructive than in others.

The preliminary remark may be made that at first the electrolytic lesions were intentionally very small. In the case of such complicated fibre areas as the globus pallidus it is essential that the lesions should be small, and in this respect the immense superiority of the accurate technique obtainable by the stereotaxic instrument is especially seen. No method other than that which it has been my privilege to utilize can be of equal service. By tracing minute degenerations first of all it is possible to unravel the degenerations of larger lesions much more readily.

I. Rhesus 248/09.—The lesion is quite small, and placed in the anterior dorsal portion of the right putamen (fig. 1).

The area of the putamen involved in the lesion is almost exactly one-quarter of its vertical height, and one-half of its breadth. The lesion extends back from the anterior limit of the putamen to where the lateral zone of the globus pallidus begins, i.e., it involves about one-fourth of the putamen considered antero-posteriorly, as seen on horizontal section.

Degenerations.

(1) There is slight degeneration from the needle track ventrally in the external capsule.

(2) The slight degeneration from the needle track of scattered cortical fibres, mostly in the white matter underlying the gyri of the island of Reil, need not be further specified.

(3) From the site of the lesion in the putamen there is very well marked and easily followed fine degeneration in numerous bundles or pencils of fibres, all, without exception, degenerating in a ventral, caudal, and mesial direction, towards the mesial plane. The degeneration is strictly confined to fibre bundles on the mesial side of the lesion, i.e., there is no degeneration in a dorsal or lateral direction. The degenerated bundles gradually converge as they pass caudally and ventrally, and fresh bundles of normal fibres appear in their place. When the lamina medullaris lateralis is reached the affected bundles have converged towards the junction of its dorsal and middle thirds. Extremely few

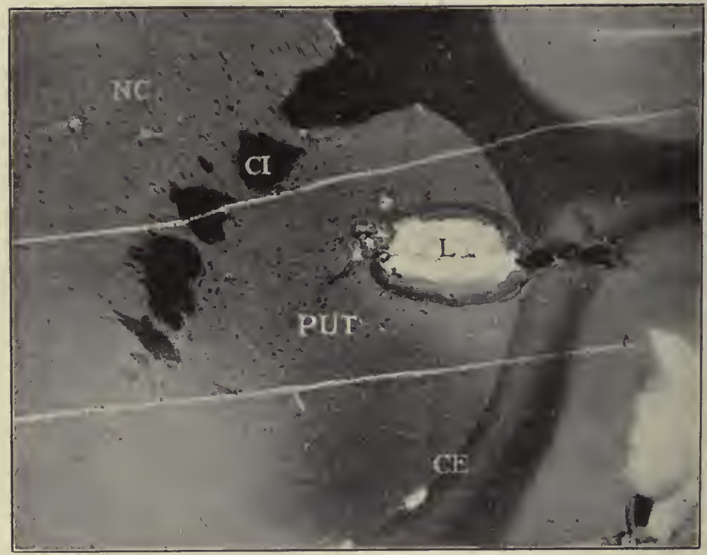


FIG. 1.—Rh. 248/09. Lesion in the anterior and dorsal portion of the putamen.

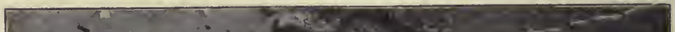


FIG. 2.—Rh. 280/09. Large lesion in putamen, which has spread round its margin.

degenerated fibres are to be seen leaving the bundles to enter the lamina; by far the greater number of them pass directly across. In the middle zone—lateral division of the globus pallidus—the affected bundles have converged still more, but the degeneration does not become diffused. The fibres keep closely together, and can be traced mesially as a narrowing pencil, gradually losing its degeneration, across the middle zone, across the lamina medullaris medialis, to end by diffusing out in the centre of the mesial division of the globus pallidus. By this time complete new bundles have taken their place in the putamen and lateral zone of the globus pallidus. None of the degenerated fibres crossing the mesial lamina pass either dorsally or ventrally in it. As the degenerated pencils travel caudally and ventrally, they gradually diminish in quantity, particularly after reaching the middle zone.

(4) None of the degenerated fibres reach the optic thalamus. None of the degenerated putamen fibres enter the internal capsule. There is no degeneration in the ansa lenticularis.

II. Rhesus 280/09.—The lesion is large, and as it were double. It occupies the whole of the lateral portion of the putamen and extends mesially half way across the nucleus, destroying vertically at least a third of it. It is mainly the anterior portion of the putamen that is involved in the lesion. In addition the bubbles of gas have made their way anteriorly and dorsally, round the external capsule, separating it from the putamen and destroying the margin of the latter. The lesion has cut across a considerable number of cortical fibres entering the internal capsule on the anterior side (fig. 2).

Degenerations.

(1) The degeneration in the external capsule passes ventrally but soon disappears, however, and is not so much as might be expected considering the position and degree of the lesion.

(2) There is marked degeneration of cortical fibres from the dorsal aspect of the lesion, many passing outwards to the cortex and others turning across the corpus callosum.

(3) There is abundant degeneration of fine fibres in the putamen, in bundles all passing mesially and at the same time ventrally and caudally. The amount of degeneration from the lesion in the putamen is exactly proportional to the size of the lesion, as is also the case in Rh. 248, showing that the degeneration originates in the putamen. The degenerated bundles occupy at least one-third of the vertical height of the nucleus, and can be traced easily across the lateral medullary lamina, across the lateral zone of the globus pallidus and the mesial lamina, to the centre of the mesial zone of the globus pallidus. As they traverse the nucleus they converge but keep in bundles even where the fibres are closely amassed together, gradually diminish in quantity of degenerated fibres, and diffuse out well across the mesial zone. They give off a few degenerated fibres to the lateral lamina—only a small proportion of the total—and only one or two to the mesial lamina. They cannot be traced beyond the globus pallidus. They do not enter the ansa lenticularis.

(4) There is a slight degeneration from the putamen across the upper third of the internal capsule into the caudate; numbers of healthy fibres come in the reverse direction.

(5) There is marked coarse degeneration of a large number of capsular fibres, readily traceable because of its striking contrast to the fine degeneration of putamen fibres. As they run side by side the two types can be easily distinguished (fig. 3). The degenerated capsular fibres do not give off any to enter either of the laminæ medullares. A few which pass from the capsule at these points are found on serial section to be aberrant bundles which converge on the main body of degenerated fibres a little further ventrally. No degenerated fibres enter the globus pallidus from the capsule.

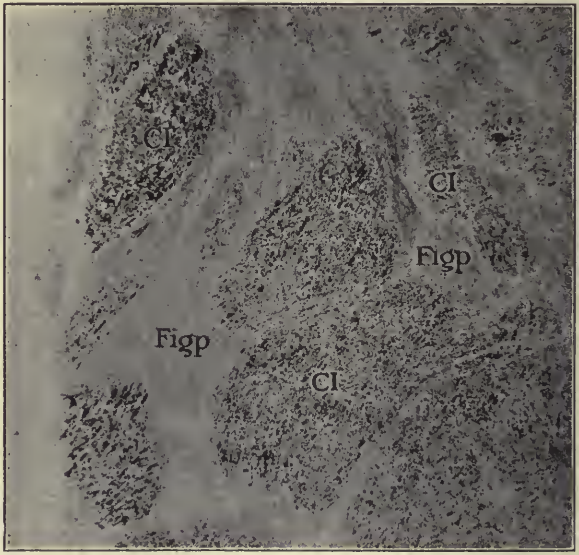


FIG. 3.—Rh. 280/09. Contrast between coarse capsular degeneration and fine internuncial fibre degeneration (scarcely visible with this magnification).

III. Rhesus 292/09.—The lesion is intentionally small, and almost identical with that of Rh. 248.

Degenerations.

(1) The usual putamen degeneration is present. All degenerated fibres pass in a caudal, ventral, and mesial direction; none degenerate in a dorsal, oral, or lateral direction. The degenerated pencils of fibres can be traced to the mesial zone of the globus pallidus; they give off very few fibres to pass into either of the laminæ. There is no degeneration into the optic thalamus or caudate, or of the ansa. The amount of degeneration from the putamen lesion is proportional to its size.

(2) One or two fine bundles of degenerated fibres are seen apparently entering the putamen from the external capsule in its dorsal and anterior section. The presumption is that these have degenerated from the needle track, for they are well beyond the degenerated putamen area and they may be of putaminal origin and have coursed on the surface of the putamen. They skirt the internal capsule and apparently enter it. At the most there are about three such bundles, and they are very small.

IV. Bonnet 316/09.—The lesion is further back in the putamen, and is of interest because of its propinquity to the lateral medullary lamina (fig. 4).

Degenerations.

As the lesion is rather small the degenerated putamen bundles of internuncial fibres cannot be traced so far, but they are at their maximum when they cross the lateral medullary lamina, whence it is easy to determine that in this instance no fibres of these bundles leave the latter to pass dorsally or ventrally in the lamina. Healthy laminal fibres can be seen passing through some of the degenerated pencils.

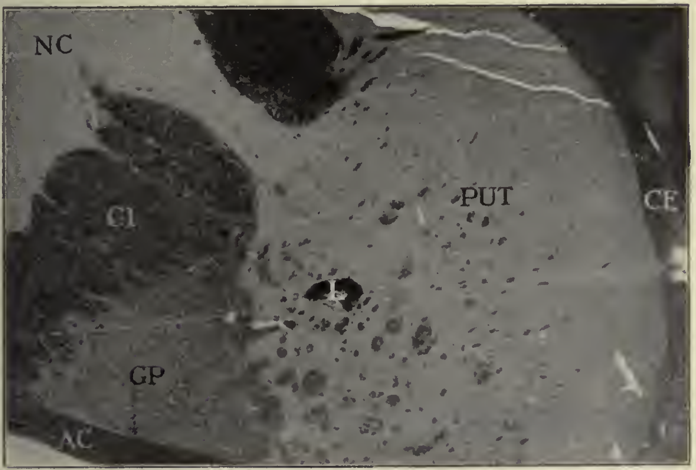


FIG. 4.—Bonnet 316/09. Small lesion in putamen, near the lateral medullary lamina.

V. Rhesus 348/10.—The lesion is in the corona radiata just dorsal to the anterior extremity of the internal capsule; it has in no way implicated the putamen, while it has caught a large number of capsular fibres from the operculum and lower motor area.

Degenerations.

(1) There is gross capsular degeneration, not, of course, complete. The degenerated fibres are coarse and easily followed. No degenerated capsular fibres enter either the lateral or the mesial medullary lamina. No degenerated

fibres enter either the lateral or the mesial zones of the globus pallidus. None enter the putamen.

(2) There is marked degeneration of associational cortical fibres in various directions.

(3) A very slight descending degeneration occurs in the external capsule.

(4) Incidentally, it is seen that a considerable degeneration of fibres in the corpus callosum is present; most make their way to the opposite cortex, but a fair number turn and enter the opposite internal capsule.

(5) A few degenerated fibres "cut the corner" of the putamen to enter the internal capsule.

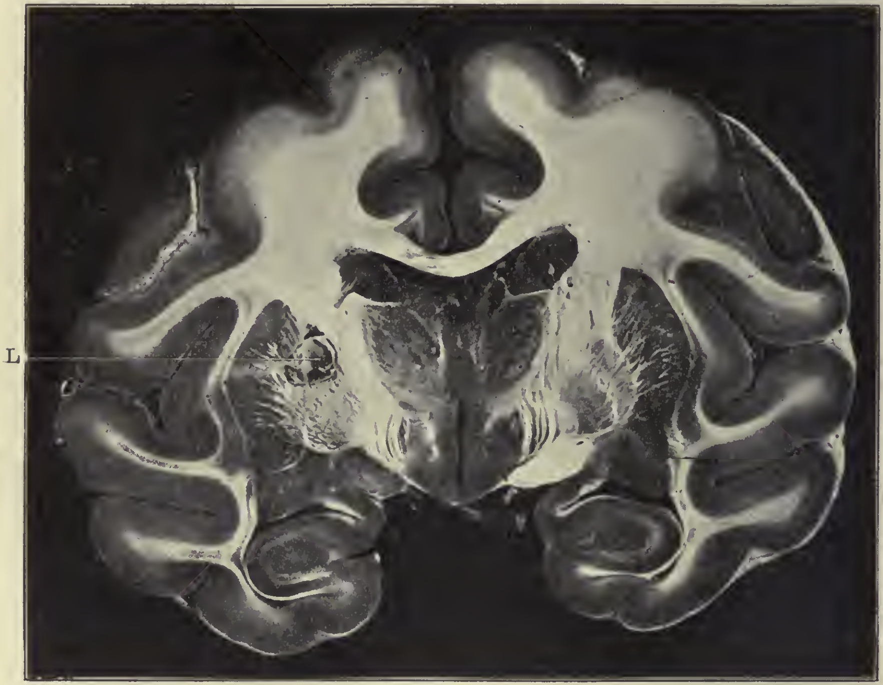


FIG. 5.—Rh. 434/10. The lesion is mainly in the lateral division of the globus pallidus.

The results of such an experiment as this go far to show that the fibre-content of the putamen is autogenous in origin.

VI. Rhesus 434/10.—The lesion occupies the dorsal anterior portion of the lateral zone of the globus pallidus in its whole transverse extent, as well as the adjacent mesial portion of the putamen and the lateral portion of the mesial zone of the globus pallidus. It has completely destroyed the dorsal half of the lateral medullary lamina, and impinges very slightly on the internal capsule about the junction of its dorsal and middle thirds (fig. 5).

Degenerations.

(1) There is slight but definite degeneration of some lenticulo-caudate fibres from the lateral zone of the globus pallidus across the internal capsule. A much greater number of healthy fibres come in the opposite direction.

(2) A fine degeneration passes ventrally in the crescentic lateral lamina, but only in small quantity does it reach the base of the lamina. Caudal to the lesion new healthy fibres soon appear in the lamina. A large number of fine fibres entering the nucleus by the lamina are degenerated; they do not follow the lamina in its whole extent, but leave it to pass into the putamen and the lateral zone of the globus pallidus; they are internuncial fibres from the caudate.

(3) There is considerable degeneration of fine bundles crossing the middle lenticular zone radially, below and behind the level of the lesion, and running mesially into the mesial zone; some of these gradually edge towards the capsule and cross it obliquely, reaching the level of the mesial zone before they start to cross; they can be followed into the lateral and ventral sections of the optic thalamus (strio-thalamic fibres). The granulation in these fibres, though fine, is perhaps not quite so fine as in the pure putamen degenerations.

It is noteworthy that considering the extent of the lesion none of the involved fibres seem to travel far; they are all short; the longest are the strio-thalamic. A number of the radial degenerated bundles, towards the centre of the nucleus, do not pass the mesial zone; after reaching well across it they diffuse out.

(4) In addition to the radial degeneration there is well-marked degeneration of transverse fibres in the middle lenticular zone, i.e., fibres more or less parallel to the course of the lateral medullary lamina. Their calibre is somewhat coarser, and their degeneration is more scattered or diffused; they can be traced ventrally and posteriorly to the ventral part of the middle zone, where most of them are brought together, and then turn again in a mesial direction as the ansa lenticularis. The degeneration of these tranverse fibres is just as marked as the degeneration of the radial fibres.

(5) Most of the radial fibres crossing the internal capsule obliquely are seen to be making their way to the corpus subthalamicum. It is clear that none of these radial fibres blend with the internal capsule in its basal third.

VII. Rhesus 450/10.—The lesion is analogous to that in Rh. 434, but it has invaded the internal capsule somewhat (fig. 6).

Degenerations.

(1) The main degenerations are identical with those obtained in the preceding animal. There is marked degeneration of strio-thalamic fibres, which can be followed mesially far into the thalamus as little bundles of degenerated fibres, keeping closely together until they diffuse out.

(2) The radial and transverse degenerations are as before. More degenerated fibres enter the ansa. The degeneration in the lateral lamina soon ceases.

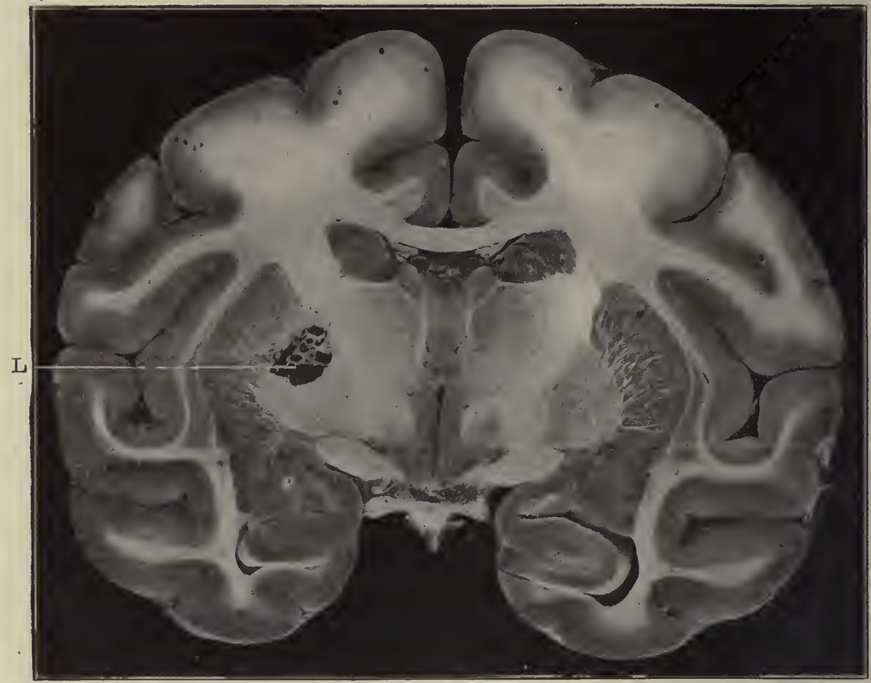


FIG. 6.—Rh. 450/10. The lesion is mainly in the lateral division of the globus pallidus.

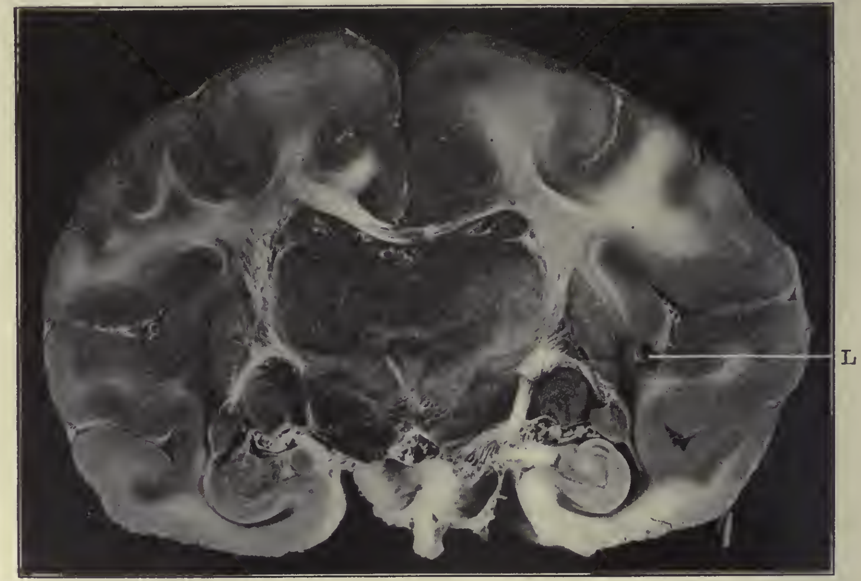


FIG. 7.—Rh. 488/10. The lesion is situated outside the putamen, at its posterior ventral extremity.

(3) Most of the degenerated radial bundles edging towards the capsule run obliquely into the corpus subthalamicum; others belonging apparently to this group can be traced in a mesial, caudal and ventral direction beyond the corpus subthalamicum apparently to the lateral part of the capsule of the red nucleus.

(4) There is well marked degeneration of the transverse fibres (part of the ansa lenticularis) in their anterior division, i.e., that part which turns round the extremity of the capsule to reach the anterior ventral corner of the optic thalamus (the *Hirnschenkelschlinge* of older writers).

VIII. Rhesus 488/10.—This experiment was made to determine whether any fibres enter the putamen from behind and below. The needle has passed through the superior temporal gyrus and the lesion is situated in the claustrum and external capsule at the posterior ventral extremity of the putamen, which itself is not touched by the lesion (fig. 7).

Degenerations.

(1) No degenerated fibres enter the putamen from its lateral side; all skirt the nucleus without entering, except a few cortico-spinal or cortico-pontine fibres which "cut the corner" of the putamen, but can very easily be shown to be merely fibres of passage.

(2) There is well marked degeneration in a dorsal direction in the external capsule, much more than in the other animals where the degeneration travelled ventrally.

(3) Various degenerations of cortical associational fibres need not be further specified.

IX. Rhesus 502/10.—The lesion is in the ventral portion of the lateral zone of the globus pallidus, destroying the ventral third of the lateral lamina and impinging on the mesial lamina. It has partially invaded the substantia innominata (figs. 8 and 9).

Degenerations.

(1) There is well marked ascending degeneration in the external capsule and in the fibres of the insula. It is interesting to note that a number of degenerated fibres enter the corpus callosum, but none at all pass into the putamen.

(2) The most caudal part of the lesion, the exact situation of which is seen in fig. 10, is excellently placed to show that some cortico-pontine fibres pass across the putamen in its caudal section merely as fibres of passage; there is no trace of any degeneration of putamen pencils. The degenerated fibres of passage are coarse and not fine.

(3) The double (transverse and radial) degeneration from the globus pallidus already referred to is particularly well seen. The transverse fibres, constituting an integral portion of the ansa lenticularis, are grossly degenerated, and readily traceable across the internal capsule somewhat obliquely to Forel's field and beyond. The radial fibres, in fine coalescing bundles, cross the capsule much more obliquely to end in the corpus subthalamicum; some of these are also found passing ventrally to the latter, skirting its ventral margin

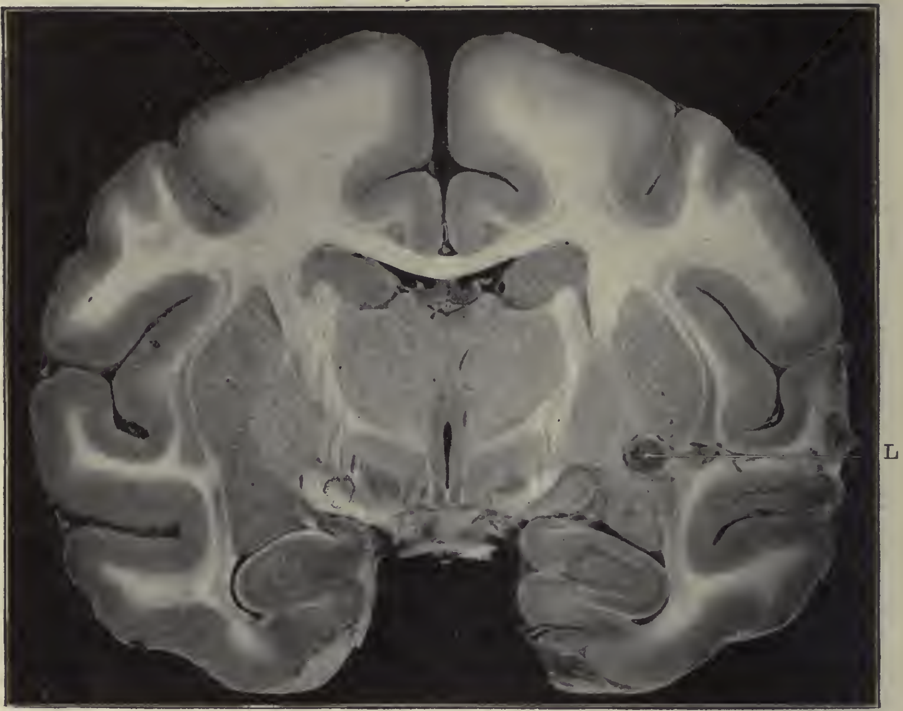


FIG. 8.—Rh. 502/10. The lesion is ventral in the putamen and globus pallidus.

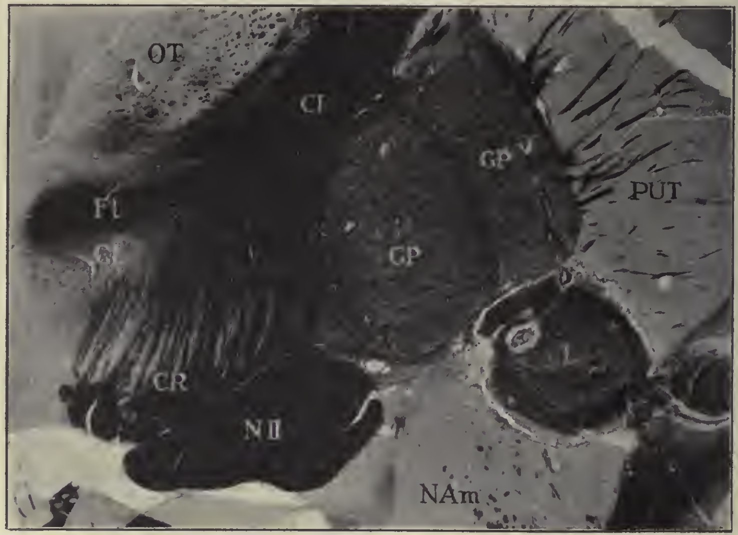
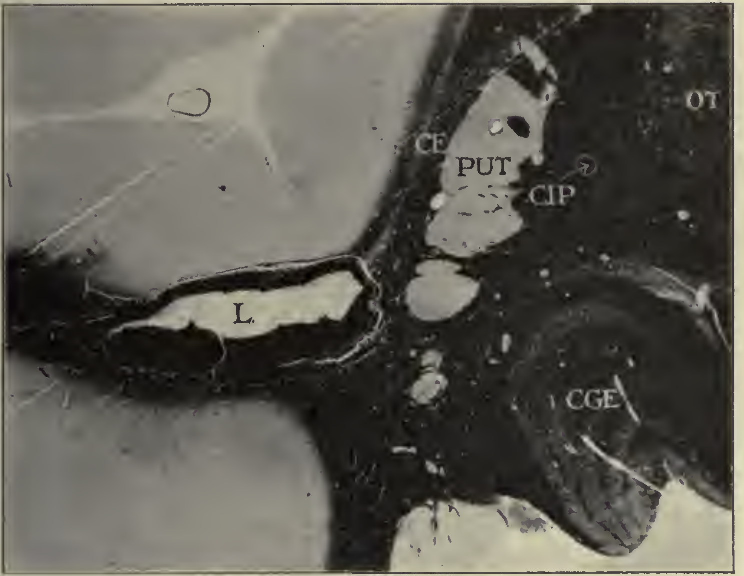


FIG. 9.—Rh. 502/10. Photograph of stained section to show exact position of part of the lesion.



[Fig. 10.—Rh. 502/10. The most caudal portion of the lesion is well placed to decide whether cortico-striate fibres enter the nucleus from below or behind.

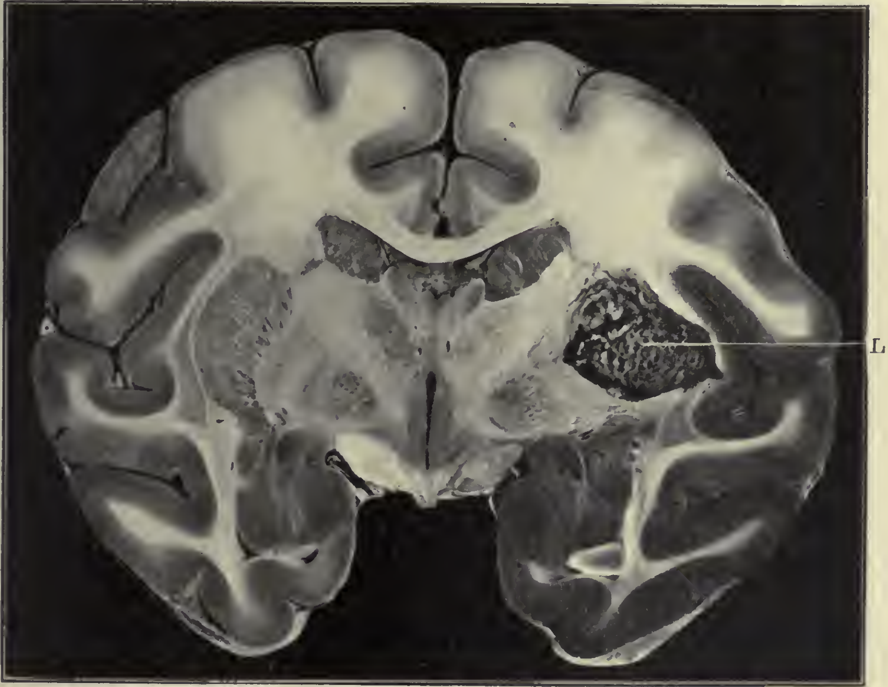


Fig. 11.—Rh. 26/11. Large lesion destroying putamen.

to end in the substantia nigra. Both of these degenerations are very complete, and owing to the integrity of the capsule they are easy to follow. The former is clearly visible travelling in a caudal and ventral direction as far as the ventral capsule of the nucleus ruber. The fibres going to the substantia nigra come from the most ventral of the ansa group. They pass mesially in a more or less horizontal fashion, and correspond to the tractus strio-peduncularis of Edinger.

(4) There is well marked but quickly disappearing dorsal degeneration in the lateral medullary lamina.

(5) There is no trace of any degeneration passing laterally in the nucleus or along the laminæ, i.e., no indication of thalamo-cortical fibres passing by the laminæ or otherwise through the nucleus to the cortex.

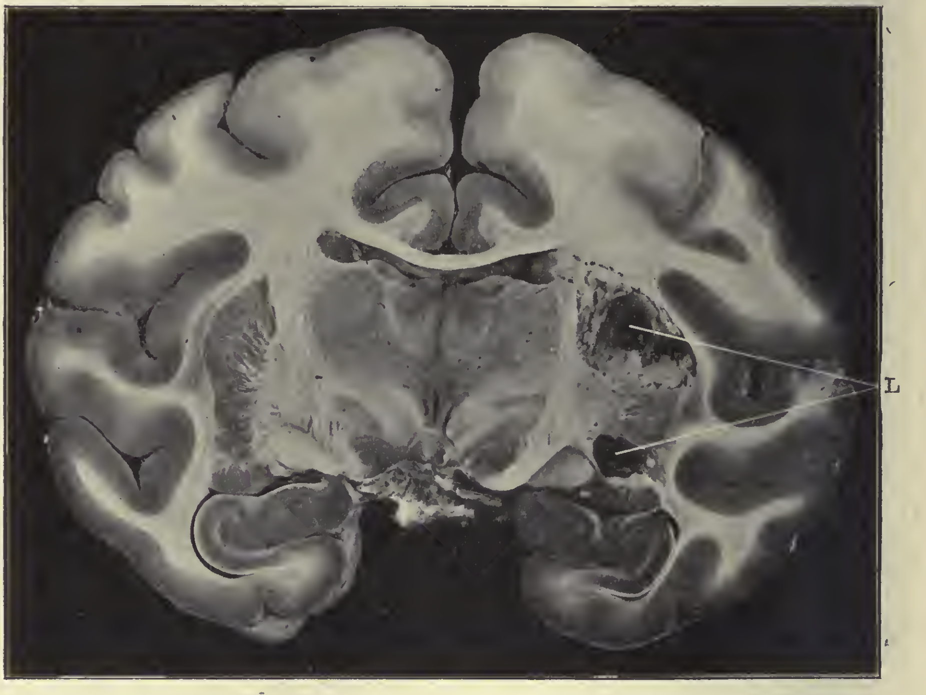


Fig. 12.—Rh .26/11. The inferior lesion is placed ventrally in the putamen and globus pallidus.

X. Rhesus 26/11.—The main lesion, a large one, has destroyed the whole of the putamen and part of the lateral zone of the globus pallidus. The external capsule is completely destroyed about its middle (fig. 11). The posterior portion of the lesion has invaded the capsule and spread across it to the caudate. A second lesion, independent of the above, is placed in almost identically the same position as the lesion of Rh. 502, and from it important degenerations can readily be followed (fig. 12).

Degenerations.

(1) The external capsule is degenerated dorsally and ventrally, but no fibres leave it to enter the putamen, in front of, or behind the main lesion, except one or two small bundles which cross to join the internal capsule. A solitary degenerated fasciculus was seen apparently entering the putamen from the external capsule and so remaining.

(2) Certain cortical associational fibres that are degenerated need not be further specified.

(3) There is well marked, fine degeneration in the region between the caudate and the optic thalamus—the stratum subcaudatum of Sachs.

(4) There is considerable degeneration of strio-thalamic fibres passing mainly into the nucleus lateralis, but also, in less degree, beyond it.

(5) The typical degenerations of the ansa lenticularis across the capsule to Forel's field and beyond, to the capsule of the nucleus ruber, are obtained, as well as the radial degeneration of fine bundles more obliquely across the capsule to the corpus subthalamicum (strio-luysian fibres), and to the substantia nigra.

(6) There is no unequivocal evidence of degeneration spreading laterally in the putamen from the ventrally placed subsidiary lesion above noted.

(7) Some degenerations of cortico-thalamic fibres need not be further specified.

XI. Rhesus 96/11.—The lesion is a double one; the chief part is in the middle of the putamen and the lateral zone of the globus pallidus; an extension from this has spread dorsally across the internal capsule; the second lesion, from which important degenerations can be traced, is situated in the ventral part of the globus pallidus, close to, but entirely independent of the neighbouring internal capsule (fig. 13).

Degenerations.

(1) In the globus pallidus both radial and transverse degenerations are pronounced, and readily distinguishable. The former consists of a fine degeneration of converging pencils of fibres; some are merely internuncial fibres, passing from the lateral to the mesial zone of the globus pallidus; others, the majority, can be followed into and through the capsular fibres, which are easily separable owing to their relatively large calibre, to the regio subthalamica. Most pass to the corpus subthalamicum; some travel further mesially, either through or round that body, to diffuse out just in front of the area where the tractus cerebello-tegmentalis passes into the nucleus ruber. It is difficult to say whether they effect any definite union with the nucleus ruber. A number of fine degenerated fibres, belonging to this group, are also traceable into the substantia nigra.

The second or transverse degeneration of rather thicker, medium-sized fibres, which at first are less compactly arranged, consist of two parts, an anterior and a posterior. The latter, constituting the major part of the degenerated fibres, can be followed with ease more directly across the internal capsule as Forel's lenticular bundle (H_2) into Forel's field (fig. 14). Here the

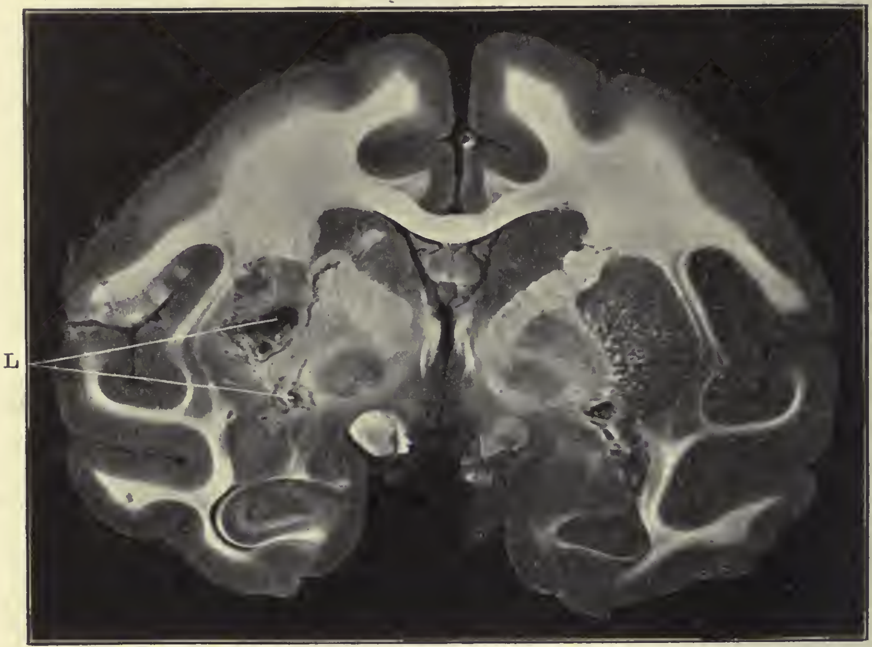


Fig. 13.—Rh. 96/11. Double lesion, both dorsal and ventral in the nucleus lentiformis.

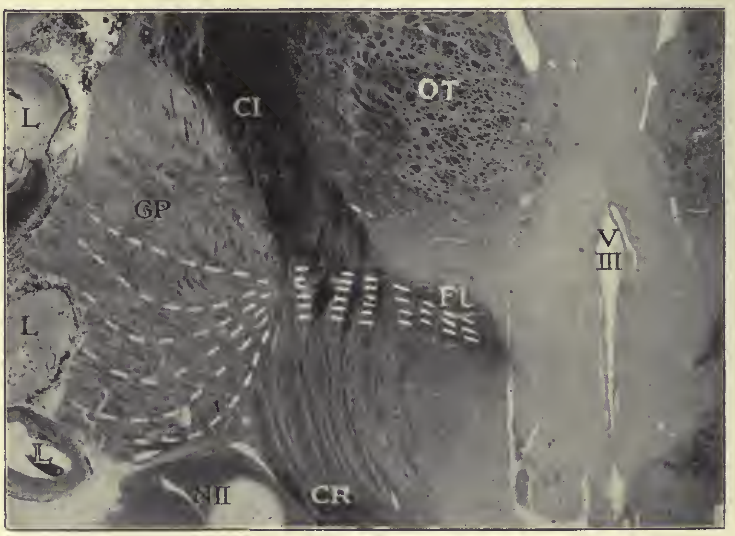


Fig. 14.—Rh. 96/11. The dotted white lines indicate the course of the transverse ansa lenticularis from the globus pallidus to Forel's field—the dorsal capsule of the corpus sub thalamicum.

fibres have converged more and the degeneration is consequently intense (fig. 15). This tract of fibres passes mesially across the field and partially subdivides. The more dorsal fibres appear to end in a sort of rounded "nucleus" near the middle line (though from this "nucleus" some fibres pass ventrally to join the others), while the more ventral portion, somewhat larger, passes ventrally, caudally and mesially, and is definitely traceable to the lateral and ventral capsule of the nucleus ruber, where the degeneration ends. The anterior portion of the transverse degeneration, less in amount than the posterior, is seen to course round the ventral end of the internal capsule, passing between its fibres only in part, to reach the most anterior lateral and ventral corner of the optic thalamus. Of this anterior group, not a few, nevertheless, once they have crossed to the thalamus, turn ventrally and can be traced eventually to join the main posterior group in Forel's field.

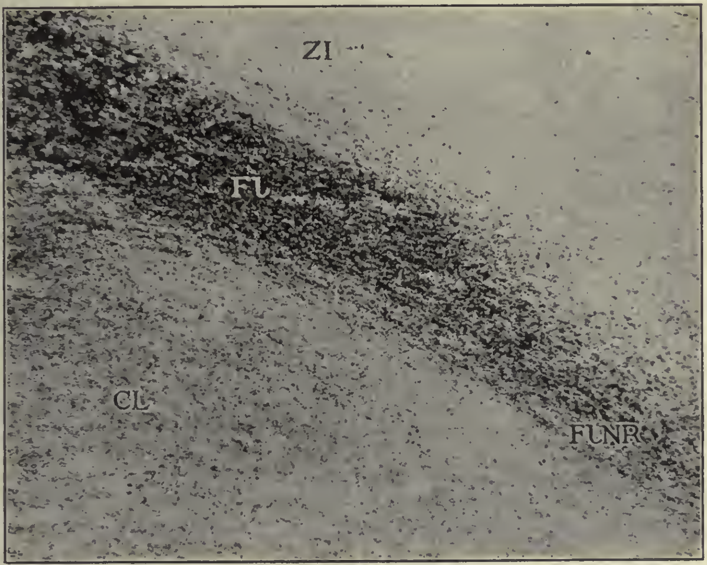


FIG. 15.—Rh. 96/11. Intense degeneration of Forel's lenticular bundle from a lesion of the globus pallidus. A portion of it passes to the capsule of the nucleus ruber.

(2) Strio-thalamic fibres are severely degenerated. They cross the capsule more or less at right angles, and diffuse out mainly in the nucleus lateralis, but some travel further, in small bundles, mesially across the thalamus to the neighbourhood of the median nucleus.

(3) The stratum subcaudatum of Sachs contains many fine degenerated fibres.

(4) Anterior to the main lesion, degeneration is traceable in both medullary laminæ. This passes dorsally in each instance, and can be seen to reach across

the upper third of the capsule to the nucleus caudatus, more particularly in the case of the mesial lamina in this instance.

(5) There is a well-marked fine degeneration along the dorsal aspect of the anterior commissure.

(6) A certain number of cortico-thalamic fibres are degenerated from the upper capsular lesion and are traceable into the ventral section of the thalamus. Across the mesial part of the zona incerta a few degenerated fibres are seen which have passed ventrally through the thalamus.

XII. Rhesus 116/11.—The main lesion is placed in the ventral part of the lenticular nucleus, extending over two-thirds of the nucleus in an antero-posterior direction. It has passed beyond the strict limits of the nucleus ventrally, invading the dorsal portion of the nucleus amygdalæ external to the optic tract, in the area of the substantia innominata sublenticularis of Reichert (fig. 16).

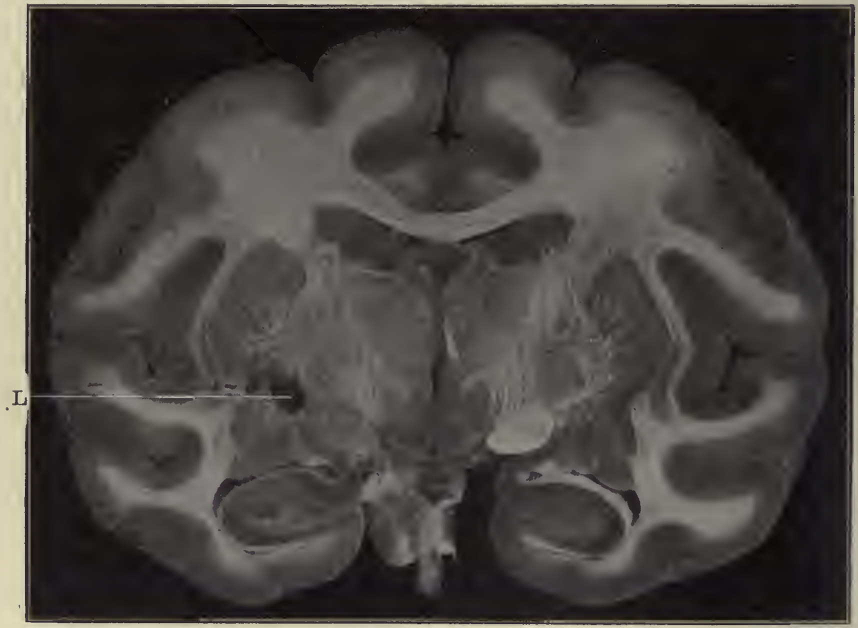


Fig. 16.—Rh. 116/11. The lesion is ventral in the lenticular nucleus.

Degenerations.

(1) There is considerable degeneration of lenticulo-caudate internuncial fibres, of fine calibre, passing from the putamen round the capsule to the caudate nucleus. Similarly there is much degeneration of fine internuncial fibres in both medullary laminæ. Some in the lateral lamina pass across the

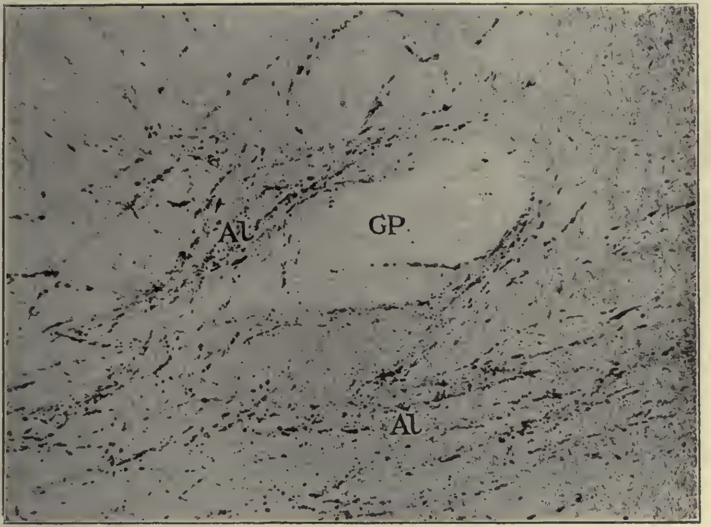


FIG. 17.—Rh. 116/11. Degeneration of the transverse ansa fibres in the globus pallidus, before they leave it.

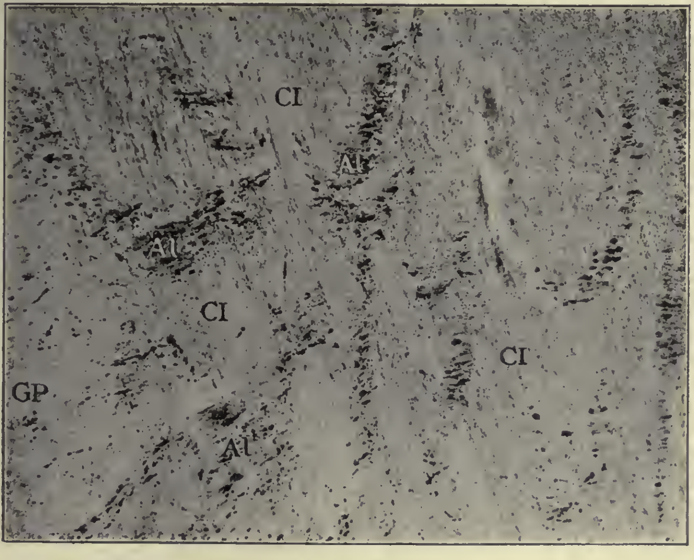


FIG. 18.—Rh. 116/11. Degenerated fasciculi of the ansa curving across the intact internal capsule.

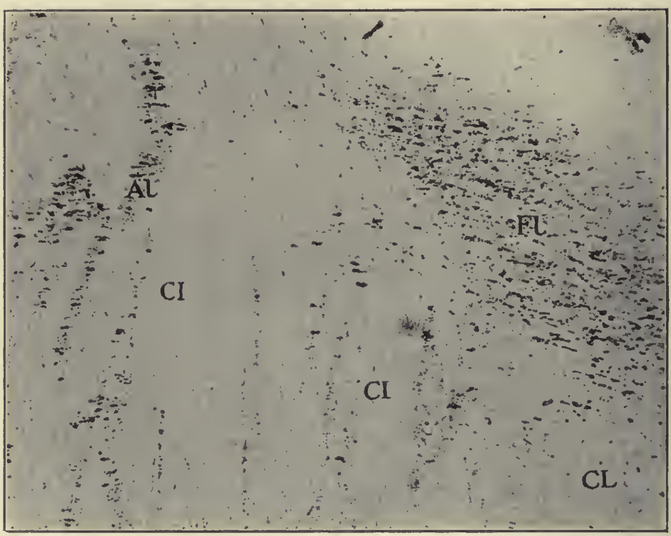


FIG. 19.—Rh. 116/11. Degenerated ansa fasciculi reaching Forel's field after curving across the intact internal capsule.

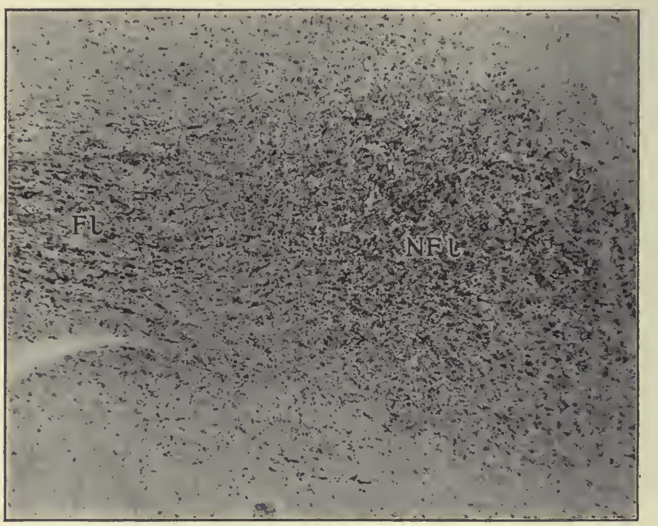


FIG. 20.—Rh. 116/11. The so-called nucleus of Forel's field, when the fibres take a different course, many passing ventrally and mesially to the capsule of the nucleus ruber.

capsule to the caudate, others turn off the lamina to enter the globus pallidus. The degenerated fibres pass dorsally in each instance.

(2) Fibres of fine calibre also pass across the capsule from the globus pallidus to the caudate in small quantity but quite definitely. These are from the lateral part of the lateral zone of the globus pallidus only.

(3) There is gross degeneration of the ansa lenticularis, and its fibres, medium in size, are very well seen as they converge towards the internal capsule, crossing it in more or less parallel curving fasciculi to enter Forel's field (figs. 17, 18, 19), across which they course mesially, partially subdividing into two groups: some end in a rounded "nucleus" at the mesial extremity of Forel's field (fig. 20), while the majority pass caudally, ventrally and mesially in a somewhat diffuse bundle and end by merging in the lateral and ventral capsule of the nucleus ruber. The anterior section of the ansa lenticularis, as described in Rh. 96, can be seen turning round the ventral extremity of the capsule to reach the antero-lateral and ventral margin of the optic thalamus. Again, some of its fibres then turn definitely in a ventral direction and join the main group in Forel's field.

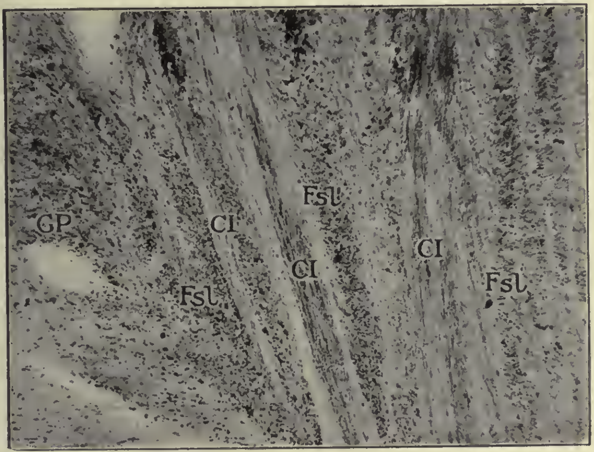


Fig. 21.—Rh. 116/11. The radial ansa fibres passing obliquely across the basal third of the capsule to the corpus subthalamicum.

(4) The radial lenticulo-fugal fibres, fine in calibre, constituting another part of the ansa lenticularis, are also grossly degenerated. They are readily traceable partly as strio-luysian fibres passing to the corpus subthalamicum (fig. 21); many, however, pass mesially to diffuse out in the area between the body of Luys and the nucleus ruber; a few pass into the substantia nigra. It is difficult to determine whether any of either part of the ansa cross the middle line; a few appear to cross in the commissure of Forel to reach the opposite nucleus ruber.

(5) There is marked degeneration of fine fibres along the dorsal aspect of the anterior commissure.

(6) There is a notable degeneration of Meynert's commissure as it lies just posterior to the optic tract. The degeneration is in an anterior and mesial direction from the lesion.

(7) There is no evidence of lateral degeneration from the lesion, in any fibres of the putamen (fig. 22).

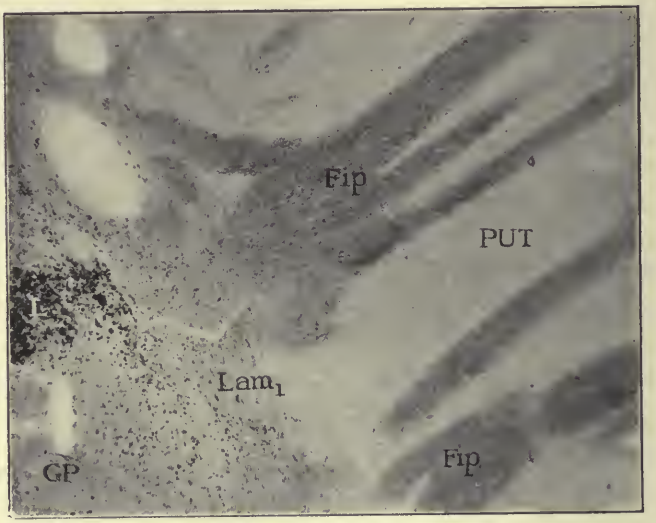


Fig. 22.—Rh. 116/11. Absence of lateral degeneration from lesion in nucleus.

Chapter III.—Analysis of Anatomical Results of Personal Researches.

A study of the small and strictly localized lesions produced according to the technique employed for the purposes of this investigation, shows that in several important respects experimental data serve to confirm and elaborate certain views as to the anatomical relations of the corpus striatum hitherto not received with any approximation to unanimity.

The fibre system of the corpus striatum may be divided into four main groups:—

(1) Fibres arising and ending within the corpus striatum (internuncial).

(2) Fibres arising in the corpus striatum and ending elsewhere (striofugal).

(3) Fibres arising elsewhere and ending in the corpus striatum (striopetal).

(4) Fibres passing through the corpus striatum, but arising and ending elsewhere (fibres of passage).

I. In the first group several subdivisions may be distinguished.

(*a*) *Internuncial fibres from the putamen to the globus pallidus.*—These are invariably of fine calibre, with a delicate myelinated sheath. They are massed into bundles or pencils, arising by the approximation of individual fibres, not always very close to their cells of origin, and running mesially; the anterior pencils converge as they pass in a posterior direction, while the posterior converge as they travel anteriorly; the most ventral run in a dorsal direction, the dorsal in a ventral direction, and in this fashion they all converge towards the lateral zone of the globus pallidus; here some of them diffuse out, while others pass on to the mesial zone, where they in turn diffuse out.

(*b*) *From lateral to mesial zone of the globus pallidus.*—Similarly fine myelinated fibres arise in the lateral zone of the globus pallidus and cross mesially in radial bundles to the mesial zone.

(*c*) *From caudate to putamen.*—Many fine internuncial fibres pass across the dorsal third of the internal capsule from the nucleus caudatus to the putamen, while others reach the lateral zone of the globus pallidus.

It is perhaps worthy of note that distinctly fewer fibres pass from the putamen to the caudate than in the reverse direction; and this is true also of the connexions between the globus pallidus and the caudate.

The composition of the laminæ medullares.—In the present series of experiments lesions have been placed both at the dorsal and the ventral extremities of the laminæ medullares. In one or two instances a degeneration has been obtained extending from end to end of the lamina; as a rule, however, the degeneration takes place along a limited length, the affected fibres then turning either into the putamen or the globus pallidus. Even the longest degeneration obtained is essentially of a finely granular type, indicating the small calibre of the laminal fibres—an important consideration. The lateral lamina is composed in great part of caudate associational fibres passing in both directions. Some of the putamen-globus pallidus fibres enter into its constitution for a short distance. The mesial lamina, similarly, is composed of short connecting fibres passing both dorsally and ventrally; these are mainly internuncial fibres between the lateral and mesial zone of the globus pallidus for a part only of their course; from a lesion in its ventral extremity the dorsally passing degeneration does not, as a rule, extend to the capsule. Caudate associational fibres are also found in it. Its ventral section blends with and is reinforced by a number of transverse, slightly thicker, fibres, termed by Dejerine [17] supplementary medullary laminæ, which go to form part of the ansa lenticularis, to be subsequently described.

It is always easy to distinguish between the fine degeneration of the short internuncial fibres and the coarse degeneration of cortico-spinal fibres; the difference is unmistakeable. Laminal fibres running close to or passing through the capsule can readily be separated from the latter. The experimental evidence here furnished, therefore, negatives the view of Obersteiner [60] and others, who place in the laminæ thalamo-cortical fibres in part of their course, and that for two reasons. Firstly, as has just been remarked, the laminal degeneration is always one of fine-calibred myelinated fibres; and, secondly, in this series of experiments, no fibres have been seen passing corticalwards along the laminæ and so out of the nucleus. In fact, no indication of degeneration passing laterally, ventrally or dorsally out of the globus pallidus or putamen (except at their extremities) from lesions in various parts of these nuclei has been obtained. The conclusion is important, and reference will be made to it again immediately. Dejerine [17] states that from lesions of cortico-pontine, cortico-thalamic, and cortico-bulbar projection-fibres in man there is pathological evidence that fibres, not of lenticular origin, pass from the cortex by the lamina medullaris medialis to the corpus subthalamicum. I have obtained no experimental proof of the existence of these fibres in apes.

II. In the second group there are also important subdivisions.

(*a*) *Strio-thalamic fibres.*—These constitute the minor portion of striofugal fibres to the optic thalamus and regio subthalamica. They are derived from the mesial groups of radial bundles of the globus pallidus, and cross the internal capsule obliquely in its basal third to reach the lateral and ventral sections of the thalamus. They can be traced passing mesially across the thalamus and diffuse out in the neighbourhood of the internal nucleus; a fair number, however, do not extend beyond the nucleus lateralis. Although Dejerine [17] regards the strio-thalamic group as arising in part from the putamen and caudate, I have failed to trace any degeneration into the thalamus from lesions strictly confined to the putamen. Caudate-thalamic fibres perhaps exist in small quantity. Probst [62], however, could not find any after lesion of the caudate, and my own experiments have failed to reveal certain evidence of their existence. Similarly, Grünstein [35] could find no trace, in rabbits and dogs, of caudate-thalamic fibres from lesions in the caudate. A group of fibres belonging to the ansa lenticularis, and corresponding to the *Hirnschenkelschlinge* of older writers, is, strictly speaking, part of the strio-thalamic system, since it passes from the globus pallidus to the optic thalamus. Reference will be made to this tract of fibres in the following description of the ansa lenticularis.

(*b*) *Strio-subthalamic fibres.*—The ansa lenticularis is a somewhat complex fibre system, in which, however, certain subdivisions are readily distinguishable.

(*a*) The chief set of fibres in the ansa stands out unmistakeably as composed of fibres slightly larger in calibre than the others, which are of the same size as the internuncial fibres already described. This tract arises in the lateral and mesial zones of the globus pallidus, runs more or less at right angles to the radially disposed pencils and is distinguished in the descriptions of experiments given above as the transverse group. It passes directly across the capsule in a slight curve with the convexity dorsal, and constitutes a closely set bundle reaching and occupying Forel's field. It corresponds to the lenticular bundle of Forel (H_2). The fibres pass mesially across Forel's field and form a sort of nucleus (*noyau du champ de Forel*—Cajal [13]) at a point where the general direction of the fibres changes slightly from a latero-mesial to a more antero-posterior direction. Many then pass ventrally and caudally and can be definitely traced to end in the ventro-lateral and ventral capsule of the nucleus ruber (figs. 23, 24). It seems possible, from one or two of my experiments, that a few fibres continue across the mesial plane by the decussation of Forel to reach the contralateral red nucleus.

This is the main group in the ansa lenticularis, and the definiteness of the anatomical connexion between the globus pallidus and the nucleus ruber is of considerable importance. It is easy to distinguish these fibres from those of the capsule, indeed from any other tract in the neighbourhood.

Von Monakow [56] states that the ansa is derived mainly from the putamen, but for apes this is certainly incorrect, as I have never found degeneration in the ansa from lesions confined strictly to the putamen. In a case examined by Tarasewitsch [75], the ansa was intact though there was a large lesion in the putamen. Grünstein [35] found a few degenerated fibres in the ansa from putamen lesions (dogs). Von Monakow [56] also

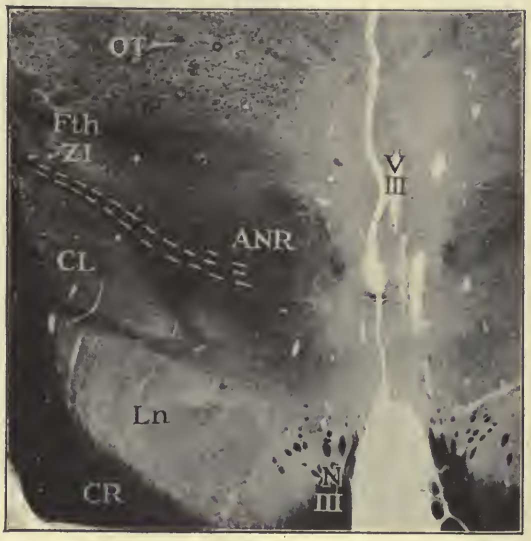


Fig. 23.—Rh. 116/11. The white dotted lines indicate direction taken by lenticulo-rubral fibres.

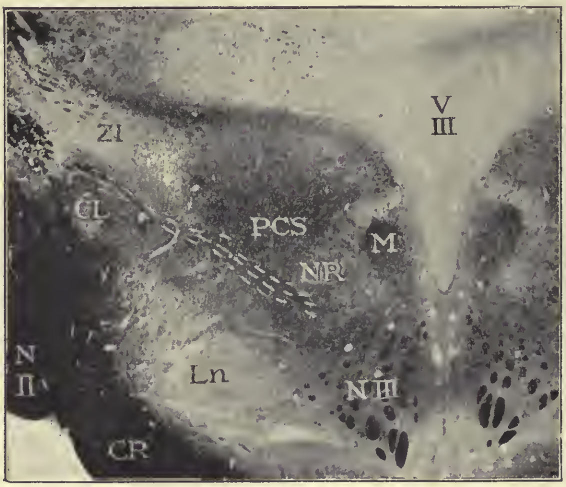


Fig. 24.—Rh. 116/11. The white dotted lines indicate the way in which fibres of ansa, from the globus pallidus, reach the capsule of the nucleus ruber.

states that some of the fibres in Forel's field edge dorsally across the zona incerta to reach the ventral portion of the optic thalamus, but I have not been able to satisfy myself of the existence of such fibres in apes. Sachs [67] was able to put a small lesion in Forel's field by the methods utilized in this series of experiments, and he found that from it a mesial degeneration passed caudally, ventrally and mesially to the ventral capsule of the nucleus ruber. Dejerine [17] admits the independence of the ansa and capsular fibres, and describes the former as reaching the capsule of the nucleus ruber in man. Edinger [21] mentions he has found negative evidence of the existence of the same connexions in the dog; after complete cortical extirpation some fibres running with the otherwise entirely degenerated cortico-rubral tracts remained; they were seen to be fibres passing from the corpus striatum to the capsule of the red nucleus. Flechsig [25] and v. Bechterew [5] had previously suspected the existence of this important relation. Cajal [13] states very positively that Forel's bundle and field consist of fibres of capsular origin. "Les auteurs considéraient ce cordon comme une dépendance du corps strié et un système tout à fait étranger au pédoncule cérébral. C'est le contraire qui est précisément la vérité. Il est tout simplement un groupe considérable de collatérales issues à angle droit du trajet des fibres motrices du pédoncule cérébral." He makes the absolute statement that no fibres of the lenticular bundle cross the capsule entirely. It is impossible, nevertheless, to subscribe to these views, which are completely refuted by my own and other experimental evidence. Cajal agrees that the fibres of Forel's field almost certainly reach the capsule of the red nucleus, and remarks that "nous ne cacherons pas que l'hypothèse d'une terminaison totale ou partielle du cordon de Forel dans le noyau rouge est loin de nous déplaire, car elle comble une lacune laissée par l'observation anatomique." Probst [64] also holds that the bundle in question is of lenticular origin, as did Forel [27] originally, followed by Mahaim [50] and v. Monakow [55]. It may be mentioned in passing that no degeneration has been found in Forel's field in amyotrophic lateral sclerosis. Both Probst and v. Monakow state that the lenticular bundle of Forel (the dorsal capsule of the corpus subthalamicum) passes mesially and ventrally to the tuber cinereum, forming a fasciculus tuberis cinerei. But I can find no proof of such connexions in these experiments on apes. Probst even states he has traced fibres across to the corpus geniculatum externum of the opposite side.

In v. Monakow's [57] recent monograph on "Der rote Kern, die

Haube, und die Regio subthalamica," no reference to the possibility of a connexion between the corpus striatum and the red nucleus is given, nor is it indicated in any of v. Monakow's diagrams—an omission (unless a reference has been overlooked) which is curious in view of the above mentioned investigations of previous observers and of the fact that there is a description of the nucleus ruber and its relations in the cat, dog, ape, &c., in the monograph.

Allusion has been made above to a more anterior portion of the ansa lenticularis composed of fibres of similar calibre, which edges round the mesial extremity of the internal capsule to reach the ventrolateral margin of the optic thalamus anteriorly. It constitutes the most anterior part of the transverse ansa fibres, and is of smaller dimensions than the other. While some of its constituent fibres do pass somewhat vertically in the thalamus, others turn ventrally once they have reached it and can be traced eventually to join the main caudal group in Forel's field.

(β) The second division of the ansa lenticularis is composed of slightly finer myelinated fibres arising from the radial bundles of the globus pallidus. They are ventral to the striofugal group to the nucleus ruber just described, and they edge across the basal third of the capsule much more obliquely. They can be traced across the capsular fasciculi as the latter extend into the crus. The great majority pass into the corpus subthalamicum (strio-luysian fibres) and diffuse out in its interior. Some, nevertheless, cross it completely and make their way to the neighbourhood of the lateral capsule of the red nucleus, approaching it from in front. It is difficult to determine whether they effect any union with the nucleus.

A smaller number of fine fibres pass obliquely across the crus in a mesial direction, ventral to the corpus subthalamicum, o reach the locus niger.

Edinger [21] describes fibres of capsular origin entering the body of Luys, but they have not been demonstrated in my series of experiments. Cajal [13], similarly, alludes to capsular fibres, derived solely from the ventral part of the cerebral peduncle, and entering the body of Luys, but elsewhere he says that it is possible they are really striofugal fibres. The ventral fibres proceeding from the mesial globus pallidus to the substantia nigra are less in number than might be supposed from the comparative prominence assigned them by Edinger, who gives them the name of tractus strio-peduncularis. No evidence of the occurrence of such fibres in man has as yet been advanced, according to Dejerine [17].

By way of résumé, the following account of the constitution of the ansa lenticularis as determined by experiments on apes may be given :—

It consists of two divisions, distinguishable by slight differences in the calibre of their constituent fibres. The first is made up of medium-sized fibres running transversely from the lateral and mesial globus pallidus across the internal capsule; its more anterior section reaches the lateral and ventral corner of the thalamus by rounding the ventral end of the capsule; its main posterior section forms Forel's lenticular bundle, crosses Forel's field, whence a good part of it extends ventrally and caudally to reach the ventral capsule of the red nucleus. The second is constituted by fine fibres from the radial bundles of the globus pallidus, which edge obliquely across the basal third of the capsule; the majority (mostly dorsal and middle bundles) end in the corpus subthalamicum, but some cross this mesially and turn caudally to end, apparently, in the immediate neighbourhood of the anterior capsule of the red nucleus; others (a few ventral bundles) pass ventrally to the corpus subthalamicum, and end in the substantia nigra.

No reference has hitherto been made to certain other parts of the regio subthalamica, viz., the zona incerta and the thalamic bundle of Forel (H_1), for the simple reason that in none of my numerous experiments on the globus pallidus has any degeneration been traced into either of these areas. On the other hand, when the internal capsule has been suitably injured, there has been an evident degeneration of cortico-thalamic fibres passing mesially and ventrally along, and forming a part of, the thalamic tract of Forel (H_1). At its caudal and mesial extremity some fibres make their way to the dorsal aspect of the nucleus of Forel's field. But no degeneration has been seen to pass to H_1 from the dorsal capsule of the body of Luys (Forel's lenticular bundle), as is mentioned by Dejerine [17] to be the case. No degeneration has been found from the globus pallidus to the zona incerta. Yet Edinger [21] declares that more or less all of the fibres crossing the zona incerta come from the ansa lenticularis, an opinion to which it is impossible to subscribe, as far at least as the ape is concerned.

(c) *Striofugal fibres to the internal capsule or cerebral peduncle.*—No unequivocal proof of the passage of fibres, fine or medium, from either the putamen or the globus pallidus to the internal capsule or crus has been obtained. The general direction of the two divisions of the ansa lenticularis is always oblique to that of the cortico-spinal fibres. Sir Victor Horsley has examined my specimens independently and agrees that they furnish no evidence of such a passage.

Probst [63] has failed to find any fibres with this course. Dejerine [17] concurs in admitting the independence of the ansa and the capsule. Prus [65] thinks there are centrifugal fibres from the putamen to the crus, but offers no anatomical evidence of these, which, for that matter, the work of other investigators and myself renders more than problematical.

(*d*) *Strio-cortical fibres.*—One of the noteworthy findings in this series of experiments has been the absence of any degeneration passing laterally from the lesions in the putamen and globus pallidus. In the putamen, for instance, no trace of outward degeneration from the lesions has been noted. From laminal lesions no degenerated fibres passing by the laminæ have been traced out of the corpus striatum to the cortex. Internuncial fibres may degenerate lateralwards from lesions of the globus pallidus, but they are easily recognizable as such. Without, therefore, enlarging on this matter further, it may be stated that strio-cortical fibres are non-existent.

Apart from thalamo-cortical fibres crossing the corpus striatum—to be referred to subsequently—Probst [63] found no association fibres between the nucleus lentiformis and the cortex after experimental lesions of the former, and my results corroborate his in this respect.

(*e*) *Connexions between the corpus striatum and contralateral structures.*—In a recent communication van Valkenburg [77], working on the corpus callosum, says: "More than one preparation led me to suppose that a part of the corpus callosum serves to connect the neostriata on each side, i.e., the nucleus caudatus and putamen. But I have not been able to find . . . . a convincing proof of this. In analogy with the archistriatal commissure which connects the nuclei amygdalæ, and a possible commissure between the palæostriata in Meynert's commissure, such a connexion of the phylogenetically most recent parts of the striatum would not be improbable." It has just been remarked, however, that there is no trace in apes of fibres passing out of the globus pallidus or putamen in a dorsal or lateral direction to the white matter of the hemispheres (van Valkenburg's experiments were on mice, rabbits, and cats). There is no evidence, *a fortiori*, of striofugal fibres reaching the corpus callosum, for the ape, at least.

In one only of my experiments was there indication of fibres crossing from Forel's field by the commissure of Forel to the contralateral red nucleus. They were very few in number. Sachs [67] has found such fibres degenerating from an electrolytic lesion in Forel's field. Dejerine [17], however, says they go "probably" to the contralateral body of

Luys; but the evidence I have to offer, such as it is, corroborates the description given by Sachs.

It has been held that the corpus subthalamicum is connected with the contralateral nucleus lentiformis by the intermediation of Meynert's commissure. This view has been supported by Darkschewitsch and Pribytkow [16], as well as by v. Bechterew [5]. Dejerine [17] says he has seen degeneration of the commissure of Meynert after lesions of the globus pallidus, with integrity of the optic bandelette. In more than one of my experiments an exquisite degeneration was traceable along Meynert's commissure from one side to the other. It is, however, quite clear from a careful scrutiny of the sections in a number of my experiments that Meynert's commissure has nothing to do with the globus pallidus. Only when the lesion has impinged on the margin of the optic bandelette has Meynert's commissure degenerated. Lesions in the globus pallidus, completely destroying its ventral part, and involving the ventral ansa lenticularis, have left Meynert's commissure intact. Where it has been degenerated the fibres cross neither to the corpus subthalamicum nor to the nucleus lentiformis. The view which places the origin of the fibres of Meynert's commissure in the corpus geniculatum internum is probably correct.

III. In the third group there are again a number of separate tracts.

(*a*) *Thalamo-striate fibres.*—As none of my own lesions were placed in the thalamus, it is not possible for me to confirm or deny, on experimental grounds, the existence of thalamo-striate fibres. It is known, however, that such do occur, the association between the thalamus and the caudate being close (Edinger, Dejerine, Sachs). Reference is made to these for the sake of completeness.

(*b*) *Subthalamo-striate fibres.*—From a lesion in Forel's field Sachs [67] has found degeneration passing laterally across the capsule in its basal third, and entering the globus pallidus, where it diffused out. No degenerated fibres entered the putamen. This degeneration resulted from the involvement of fibres passing in a reverse direction in the main part of the ansa lenticularis. Similarly, Dejerine (case Gardette) was able to follow degeneration from a lesion in the regio subthalamica: (1) mesially, according to the lines already fully described, and (2) laterally, by the ansa lenticularis and Forel's lenticular bundle to the globus pallidus. It would appear, therefore, that while the ansa lenticularis and the strio-subthalamic tracts are to a very large extent striofugal, they also contain striopetal fibres. Such fibres are, no doubt, to be expected, for it is a general rule that cerebral areas of grey matter are united doubly, though not always equally, to each other, by afferent and efferent fibre-systems.

(*c*) *Cortico-striate fibres.*—The experiments herein detailed show sufficiently that the corpus striatum is independent of the cerebral cortex. A few small fasciculi may cross the dorsal, ventral, oral or caudal aspects of the putamen from the cortical side, but they are fibres of passage. With practically complete capsular degeneration no fibres have been seen to leave the cortico-spinal path and enter the lenticular nucleus by its laminæ or otherwise (fig. 25). Occasionally aberrant bundles may leave the capsule to diverge towards the lenticular nucleus, but they invariably join it again. No sign of Cajal's collaterals from the cortico-spinal system which arborize among the cells of the lenticular nucleus, and, according to him, transmit voluntary motor excitation, has been discovered. Besides, the calibre of the cortico-spinal group is distinctly larger than that of the fibres of the corpus striatum.

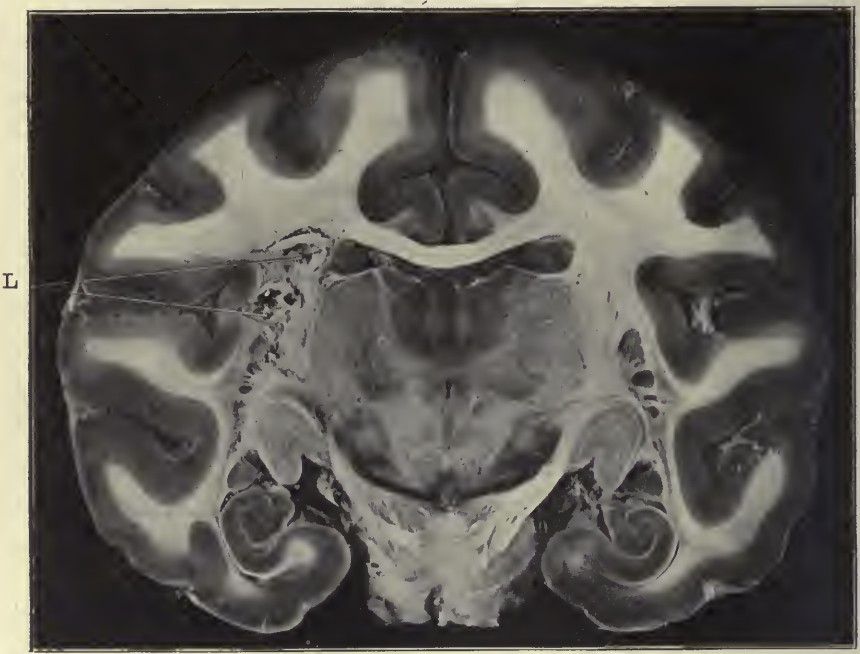


Fig. 25.—Rh. 80/11. (Not given in text.) The photograph indicates part of the comprehensive lesions made to demonstrate the independence of the lenticular nucleus. No cortico-striate fibres were found.

The consensus of opinion among investigators is in favour of the independence of the corpus striatum and the cerebral cortex. A century ago Burdach [12] showed that the appearances suggested that the putamen was not connected with the cortex, and no evidence has been adduced to combat the contention; neither strio-cortical nor cortico-striate fibres exist. Marinesco [51] alone has maintained that as a result of complete or partial destruction of the frontal lobe (in apes and dogs), fine degenerated bundles of fibres can be traced into the corpus striatum, more particularly the caudate. Apart from the inexactness of such general experiments, Cajal [13] could not find any trace of such fibres and says there are no direct cortico-striate connexions. So also Dejerine and many others. The absence of any such anatomical paths renders nugatory Mingazzini's [53] hypothesis of subordinate motor centres in the lenticular nucleus under the influence of the cortex. All the anatomical and experimental evidence goes to demonstrate the complete autonomy of the corpus striatum.

(*d*) Cajal places in the lenticular nucleus and caudate *collaterals from the fillet*, ascending sensory fibres, whose exact origin he does not further specify. There is no experimental evidence for the existence of such fibres in apes. It is perhaps scarcely worth mentioning now that the view formerly held by Flechsig [25] and v. Bechterew [5] of a participation of fillet fibres in the ansa lenticularis is quite discredited since the researches of v. Monakow [55] and Mahaim [50].

IV. There remains the final question of any fibres of passage running for part of their course through the corpus striatum.

(*a*) *Thalamo-cortical.*—The experimental evidence in this matter has already been considered. It negatives the possibility of such fibres passing in part by the laminæ of the lenticular nucleus, and is thus definitely opposed to the views of Probst [63], Obersteiner [60], and others. Tschermak [76] believed that fillet fibres made a loop-shaped excursion through the nucleus lentiformis on their way to the cortex, but assent to this view cannot be accorded. In one instance only, it should be said, have I found fibres whose relative calibre proclaimed their extra-striate origin degenerating in a lateral direction from a lesion in the lateral zone of the globus pallidus. They were not laminal fibres. In all some two or three small fasciculi were seen to contain somewhat coarse Marchi granules, and they were traced lateralwards out of the putamen. In view of the fact that identical lesions in other animals failed to reveal any such fibres, those just mentioned must be considered aberrant bundles presumably of thalamo-cortical fibres.

In number they were quite insignificant, while the fact that they passed out of the putamen a little more centrally than the fasciculi previously alluded to, which "cut the corners" of that structure, is perhaps a sufficient reason for making a reference to them at all.

(*b*) *Cortico-thalamic.*—It has been held, similarly, that some of this group pass by the laminæ medullares of the lenticular nucleus, but there is no evidence of such a route in apes.

(*c*) *Cortico-luysian.*—Dejerine [17] says that "le corps de Luys . . . reçoit de la corticalité cérébrale quelques très rares fibres qui passent par les lames médullaires du globus pallidus." However this may be in man, I cannot find them in the apes on which experiments have been made.

CHAPTER IV.—PHYSIOLOGICAL AND GENERAL CONSIDERATIONS.

The problem of the function of the corpus striatum in man, difficult as it is, is brought nearer solution by a consideration of the anatomical (human and comparative) and clinico-pathological sides of the question, each of which will be found to furnish a material contribution to the subject.

(1) It is essential in discussing the physiology of the corpus striatum to think anatomically. Admitting the not infrequent error of supposing that anatomical juxtaposition argues physiological relationship, it is, nevertheless, a more serious mistake to assign functions to an organ which it is anatomically incapable of carrying out. Now we have seen that the cardinal anatomical connexions of the corpus striatum are as follows:—

(i) It is independent of the cerebral cortex.

(ii) The putamen and caudate are closely linked to each other, and both to the globus pallidus.

(iii) The main striofugal and striopetal fibre-groups are related to the globus pallidus only, and not to the putamen and caudate directly.

(iv) The striofugal groups preponderate, and link the globus pallidus with the optic thalamus and the regio subthalamica, including the nucleus ruber, corpus subthalamicum, and substantia nigra.

(v) The corpus striatum is not connected directly with the spinal cord.

(vi) The corpora striata are, directly at least, independent of each other.

From a consideration of these anatomical data, obtained by experiments on apes, and known to be, in great part, if not entirely, identical in man, it is clear that the corpus striatum is an autonomous centre; in other words, whatever its function, that function is exercised independently of the cerebral cortex. Further, these anatomical data indicate that that function is motor in type, i.e., that it is exercised in an efferent or caudal direction. It does not, however, follow that because the main connexions are efferent the motor function of the organ is identical with, or even similar to, the motor function of the cortico-spinal system.[1]

Certain other anatomical features may here be referred to. By far the greatest number of the cells of the corpus striatum in man are small and of a more or less spindle or spherical and only slightly polygonal type, with scanty cytoplasm. It is mainly in the globus pallidus that larger cells are to be found; the former have short axons, the latter longer axons, and they belong to the striofugal group of neurons. There are not, however, in the corpus striatum large polygonal cells unmistakeably of the type of the Betz cells of the motor cortex or the ventral cornual cells of the spinal cord. Again, the calibre of the internuncial fibres is very fine, and that of the larger of the ansa fibres is less than that of the fibres of the adjacent cortico-spinal system. Without laying unjustifiable emphasis on these structural differences, they may, I think, be taken at least to suggest that the function of the corpus striatum and its projection-system is not, in man, identical with the function of the motor cortex and its projection-system.

For anatomical reasons, therefore, apart from any other considerations, the possibility of the existence in the corpus striatum of "centres" in any way analogous to those of the gyrus precentralis must be regarded as very doubtful. Brissaud [9], Halipré [36], and others, explained the phenomena of pseudobulbar paralysis by placing hypothetical centres for articulation in the corpus striatum, but Brissaud apparently imagined that the ansa lenticularis joined the cortico-bulbar and cortico-spinal systems. There is, however, no direct anatomical path to the appropriate motor nuclei from the corpus striatum. No movements akin to the movements of articulation can be obtained by stimulation of the putamen or globus pallidus in apes,[1] and we shall see later that phylogenetic evidence indicates that in man it is unlikely that the corpus striatum should possess more elaborate motor functions than in apes. Mingazzini [53] imagines, to explain the phenomena of aphasia, a "speech-motor path" from the cortical speech centre to the putamen, and a second "verbo-articulatory path" from the putamen through the globus pallidus to the crus and so to the pontine and bulbar motor nuclei. The probability certainly is that such a system is anatomically impossible.

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[1] An additional anatomical fact not without interest is that the globus pallidus and its projection-system, the ansa lenticularis, become myelinated comparatively early in fœtal life, but the significance of this fact is debateable. As the myelin appears first near the cells of origin and appears progressively towards the ends of the fibres, it may be taken to indicate the direction of the nerve impulses. It is usually held that the appearance of myelin coincides with the assumption of functional activity on the part of the fibre, but this view is not of universal applicability. Edinger [18] says it is surprising that the basal forebrain bundle does not always become myelinated early, *e.g.*, in the young frog and salamander, and holds that "if medullary sheaths are developed whenever certain portions of the brain come into active use, then there are highly organized animals which do not make use of their forebrain."

On anatomical grounds the localization of "automatic movements" in the corpus striatum, or its description as a "subcortical motor centre" whose motor function is in any way analogous to that of the motor centres of the cerebral cortex, cannot be entertained. The independence of the motor cortex and the corpus striatum, and the peculiar projection-system of the latter, make these views untenable.

(2) Evidence derived from the sources of comparative anatomy and physiology has an important bearing on the function of the corpus striatum.

In the whole vertebrate series the corpus striatum is a prominent organ. Phylogenetically, it is a very old structure, consisting of the basal part of the telencephalon or fore-brain. In fishes it consists of a palæostriatum only, corresponding to the globus pallidus of the higher vertebrates: in reptiles and birds there are additions to it in the shape of (1) the archistriatum, corresponding to the nucleus amygdalæ of the apes and man, and (2) the neostriatum, which represents the putamen and caudate nucleus. The palæostriatum or globus pallidus is the oldest part of the corpus striatum not merely phylogenetically, but also ontogenetically. Its cells develop in the fœtus in mammals earlier than those of the other divisions, while the globus pallidus and the ansa lenticularis myelinate earlier than the fibres of the rest of the striatum.

The fibre-connexions of the palæostriatum are important. In all vertebrates a well-marked and definite bundle passes from the corpus striatum to the optic thalamus and beyond. As Edinger [19] says, a fibre-system found so universally and so obvious must have a special significance; it is, indeed, primeval (*uralt*). This basal bundle or basal fore-brain bundle (*basal Vorderhirnbündel*), a tractus strio-thalamicus and tractus strio-subthalamicus in one, is essentially striofugal or centrifugal, i.e., efferent or motor, and it links the palæostriatum to the optic thalamus and to the motor centres of the mid- and hind-brain and spinal cord. According to Johnston [40] this linking of the palæostriatum to motor centres situated caudally is effected by means of the fasciculus longitudinalis medialis (posterior longitudinal fasciculus), the oral end of which is continuous with the caudal extremity of the tractus strio-thalamicus. Thus the original motor pathway from the palæostriatum is broken once in the optic thalamus, and the fibres arising here probably make connexion with widely separated motor nuclei in the brain and spinal cord. Essentially the same motor conduction path, according to the same author, is found in all vertebrates, although its functional relations may be somewhat modified in mammals on account of the cerebral cortex. Whatever be the case in the lowest vertebrates, the posterior longitudinal fasciculus in the mammalia and in man cannot have the same function as its homologue may have had as a "primitive somatic motor fasciculus." The researches of Fraser [30] (cats and monkeys) show that only a few fibres unite the fasciculus to the optic thalamus, and these are all afferent to the thalamus or centripetal.

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[1] It should be said, at the same time, that Grünbaum and Sherrington [34] obtained no experimental evidence in the chimpanzee of the existence of a cortical centre in that animal analogous to Broca's area in man.

The facts are important by analogy, for they supply another instance of cerebral function moving away from its original localization with the development of the vertebrate species. Like the ansa lenticularis, the posterior longitudinal fasciculus has, in part at least, depreciated.

Edinger, however, does not describe the original tractus strio-thalamicus and tractus strio-subthalamicus (ansa lenticularis) as extending directly beyond the subthalamic nuclei and the substantia nigra in higher mammals; at the level of the posterior colliculi the bundle, important though it is, has disappeared. Van Gehuchten [31] has described an original "tractus strio-spinalis" following the course just mentioned, but it is not clear whether he considers the posterior longitudinal fasciculus its homologue, or whether he admits that the path is really indirect. He says it has not as yet been found in mammals, in which he believes it is replaced by the cortico-spinal path.

The researches of Ariëns Kappers [1] [2], de Vries [78], and de Lange [41], in the lower vertebrates, have shown that the palæostriatum is linked to the optic thalamus and mid-brain, medulla oblongata and cord by double connexions, both efferent and afferent. Its relation to the trigeminal system in particular, both motor and sensory, seems to be very close. This is well seen in the reptilia. It is well recognized that the rule of double connexions between nervous ganglia obtains almost universally in the nervous system of vertebrates, so that while the main connexions of the palæostriatum are striofugal we cannot suppose that it is insulated from sensory stimuli in any way; on the contrary, we must conceive of the palæostriatum as a correlation-centre for various sensory impulses (olfactory, gustatory, &c.), from which passes caudally an efferent tractus strio-thalamicus, with connexions, for the execution of motor impulses. The part of the striatum associated with olfactory impressions is more particularly the archistriatum, the homologue of the nucleus amygdalæ in man. The archistriatum is connected with a tertiary olfactory path, and Ariëns Kappers thinks that even in mammals a part of the corpus striatum may subserve an olfactory function. However, be this as it may, the nucleus amygdalæ can readily be distinguished from the neostriatum (putamen and caudate) with which it is continuous only in appearance; its cell maturation is later than that of the palæostriatum and earlier than that of the neostriatum, and, as de Vries says there is doubt whether it may not really be pallial in origin, while Elliot Smith [72] has shown that at the palliostriate junction there is confusion owing to the rapid growth of (among others) the olfactory cortex in the neighbourhood of the corpus striatum, we may leave the archistriatum as not being of further interest for our subject.

Looked at from the point of view of comparative physiology, we may regard the original corpus striatum, in Elliot Smith's words, as that part of the original cerebral hemisphere whereby impressions of smell, and no doubt other sense impressions, may bring their influence to bear on the nervous mechanisms regulating movement.

The palæostriatum, then, has a projection-system which consists of the basal bundle, or tractus strio-thalamicus and strio-subthalamicus, and which is continued, according to Johnston, as the fasciculus longitudinalis medialis, or at least as a part of the latter; this is designated by him the primitive somatic motor fasciculus. It is therefore to be considered the homologue of the cortico-spinal paths of man, and is, for instance, in the fishes, the sole descending tract that can be compared to the cortico-spinal motor system of higher vertebrates.

With the progressive development of the brain the motor paths become more complex. When a pallium develops above the original palæostriatum motor centre, as in reptiles, birds, &c., the descending paths are doubled. The earliest appearance of cortico-spinal fibres separating the two parts of the neostriatum and blending with the striofugal projection-system is in the higher reptilia, according to de Lange. The state of affairs in the bird's brain is particularly remarkable. In Ariëns Kapper's view it is possible that the neostriatum of birds acts vicariously for the neopallium or cortex. In the tractus strio-mesencephalicus are mingled fibres both of striate and of pallial origin, and the suggestion is made that it is because of the necessity for economy of space in the brains of birds that such a state obtains. It should not be forgotten, however, that McKendrick [48], Ferrier [22], Mills [52], and others have shown definitely that the pallium of birds is electrically inexcitable; Ferrier obtained no movements at all; McKendrick noted simply movements of the iris and eyeball. The mammalian brain, in its turn, is very different from that of the birds and reptiles. The reptilia have an olfactory pallium; birds a visual and an olfactory pallium; the lower mammalia, a visual, an olfactory, an auditory, and a tactile pallium. With further development of the pallium afferent systems are pushed beyond the level of the thalamus and corpus striatum to reach it; and while in response a definite cortico-spinal motor system is developed the primitive motor projection-system of the corpus striatum disappears, or, rather, is reduced to the ansa lenticularis, which does not extend beyond the nucleus ruber. Its function is replaced by that of the cortico-spinal or pyramidal tracts.

In some ways there is a parallelism between the development of the corpus striatum as a whole and that of the pallium. The former, consisting originally of a palæostriatum possessing motor and correlating functions, develops by the addition of a neostriatum (putamen and caudate) which is found for the first time in the lower reptilia and increases in relative size through the lizards, birds and mammals; so in proportion to the corpus striatum as a whole the pallium develops increasingly through the vertebrate series. But the analogy does not carry us far; while the function of the pallio-spinal system usurps that of the strio-spinal system we do not know that the neostriatum abrogates the function of the palæostriatum. In fact the exact relation of these two to each other in functional activity is far from clear, that is, in the case of animals whose pallium is still comparatively insignificant.

Indeed, the relation of the neostriatum to the palæostriatum is one of the difficult subsidiary questions in a difficult subject. Ariëns Kappers, apparently, is the only investigator who has devoted attention to the matter. He believes that just as in the higher mammalia and man the pallium has taken the place of the corpus striatum as a whole, so the neostriatum (putamen and caudate) takes the place of the palæostriatum (globus pallidus) in birds. In his view, further, the connexions of the neostriatum with the thalamus is an indication that the former has functions in relation to the fillet and trigeminal systems. Whatever may be the case in birds, this view does not commend itself in the case of animals with a better developed pallium. My experiments in apes show conclusively that the neostriatum has no projection-system of its own beyond the palæostriatum; with the possible exception of a few caudate-thalamic fibres, the neostriatum is not connected to the thalamus or subthalamus at all; it is the globus pallidus which through the whole vertebrate series possesses the important projection-system. This may perhaps suggest that the corpus striatum should be considered as a physiological unit, or, rather that the functions of the neostriatum and palæostriatum are blended.

It will be understood from this brief sketch, then, that at one stage in the development of the vertebrates the thalamus and corpus striatum functioned as a brain in miniature, the latter being a correlating centre concerned with the translation of sensory into motor impulses; but, even at the best, its motor functions must have been simple compared with the complexities of the pallium of the mammalia. In the course of development the corpus striatum and its projection-system have depreciated; they have had to abandon their position of hierarchy in the field of motor activity. Thus the facts of comparative anatomy and physiology support the evidence derived from experiment. In view of the changing importance of the corpus striatum it becomes a delicate matter to allocate its function in the various animal groups; its function in man is not necessarily identical with its function in apes. Although the curious and unique features of the bird's brain demonstrate conclusively that evolution is not necessarily progressive, from the strictly motor point of view the corpus striatum seems to have been progressively shorn of its possessions; its proportionate size in man is less than in any of the lower animals, and it may be that the superman of the future will have no corpus striatum at all.

(3) We have seen that whatever function the corpus striatum once possessed there is no experimental evidence in apes to show that it exercises any motor function comparable to that of the motor cortex. There is no evidence to suggest that it is a centre for so-called automatic

movements. It is electrically inexcitable, and comparatively large unilateral lesions do not give rise to any unmistakeable motor phenomena. In short, the only proofs that it does possess a function of a motor order, in the widest sense, as we must say we should expect it to exercise in view of its phylogenetic history and the facts of anatomy, are to be obtained by a consideration of clinico-pathological data.

I have gone fully into the question of the physiology of the corpus striatum in man in my paper [82] on "Progressive Lenticular Degeneration," to which the reader is referred. It is unnecessary to recapitulate in this place; suffice it to say that in that paper arguments are advanced in support of the view that the corpus striatum is a structure which exercises a steadying influence, viâ the lenticulo-rubro-spinal projection-system, on the innervation, from the cortico-spinal or pyramidal system, of the "final common path"—the lower motor neuron, and that it is in a way concerned with the maintenance of "tone" of the skeletal muscles.

We owe to the genius of Sherrington [71] the conception of the "final common path." At the commencement of every reflex arc is a receptive neuron, which is reserved exclusively for impulses generated at one single receptive source. The motor neuron at the other end, however, receives impulses from many receptive sources. "It is the sole path which all impulses, no matter whence they come, must travel if they are to act on the muscle fibres to which it leads. Therefore, while the receptive neuron forms a *private path* exclusively serving impulses of one source only, the final or efferent neuron is, so to say, a *public path* common to impulses arising at any of many sources of reception." And again, "reflexes originated at different distant points, and passing through paths widely separate in the brain, converge to the same motor mechanism (final common path) and act harmoniously upon it. Reflex arcs from widely different parts conjoin and pour their influence harmoniously into the same muscle. The motor neurons of a muscle of the knee are the *terminus ad quem* of reflex arcs arising in receptors not only of its own foot, but from the crossed forefoot and pinna, and tail, also undoubtedly from the otic labyrinth, olfactory organs, and eyes. Thus, if we take as a standpoint any motor nerve to a muscle it consists of a number of motor neurons which are more or less bound into a unit mechanism; among the reflex actions of the organism a number can all be brought together as a group, because they all in their course converge together upon this motor mechanism, this final common path, activate it, and are in harmonious mutual relation with regard to it."

This illuminating conception of a "final common path" is not further applied by Sherrington in a detailed manner, but by implication it may be applied to the problem before us. The view which I hold of the function of the corpus striatum and its projection-system may be expressed as follows:—

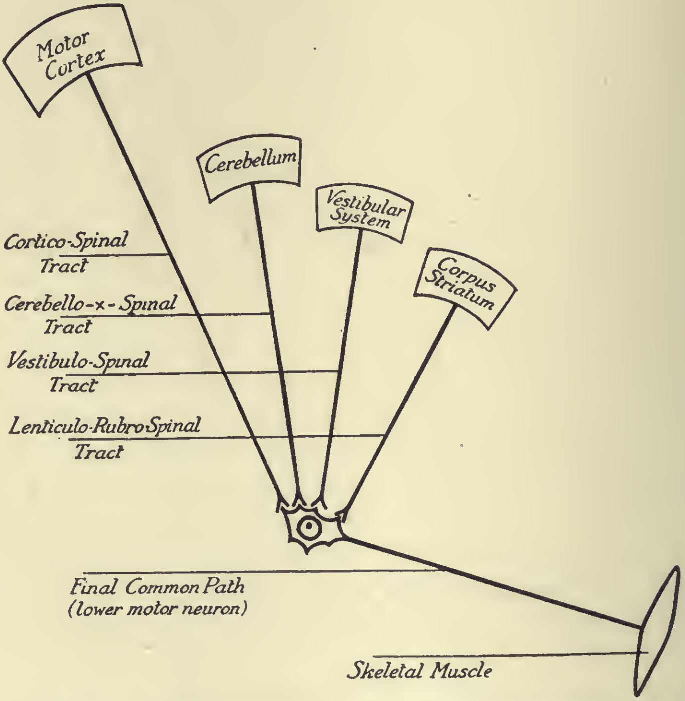

FIG. 26.– Diagrammatic representation of the various influences that act on the skeletal muscles viâ the final common path of the lower motor neuron.

Various influences act harmoniously on the final common path of the lower motor neurons: (1) The cortico-spinal motor system extends from the Betz cell "ganglion" to the arborizations round the anterior cornual cells, and its function is to innervate, or to conduct innervating impulses, originating we know not how in the cortex, to the final common path. If this system is impaired or destroyed by a lesion the result is paralysis. (2) The cerebellar system also exerts an influence on the final common path. Its ganglion is the cerebellum, from which it extends by a series of internuncial neurons to the lower motor neuron. The cerebellum exerts a co-ordinating and co-operating influence on the stream of innervation passing from the rolandic motor ganglion viâ the final common path to the muscles. The routes by which cerebellar influence is exercised are complicated; some, perhaps, may pass by the tractus cerebello-tegmentalis to the opposite nucleus ruber and so back to the spinal cord on the same side; some travel by the superior cerebellar peduncle, contralateral optic thalamus and contralateral cortex and so back to the final common path by the corticospinal system itself. In this case the latter becomes an *internuncial* common path as opposed to the *final* common path, and Sherrington makes it clear that such internuncial common paths are by no means infrequent. For the sake of simplicity, however, we shall indicate cerebellar influence in our diagram by an independent path. A lesion of the cerebellar path results in inco-ordination or ataxia, or better, dysmetria, while there is no paralysis. (3) Another important reflex path carrying impulses to act on the final common path is the vestibular. It extends from Deiters' nucleus (to which there is a private path from the labyrinth) viâ the vestibulo-spinal tract to the anterior horn-cells. An additional allied mechanism is perhaps constituted by the posterior longitudinal fasciculus, which is linked to Deiters' nucleus and also passes to the anterior horn-cells. Interference with the function of the vestibular element in the activity of the final common path results in what is called by the French school "titubation." It is of course commonly held that some at least of the cerebellar influx to the cord is transmitted by Deiters' nucleus and the vestibulo-spinal path, and this may very well be so. But it is desirable to attempt to separate cerebellar from vestibular elements in co-ordinate innervation, and for diagrammatic purposes, at any rate, one may properly be distinguished from the other. (4) Finally, there is the strio-rubro-spinal path, conveying impulses from the corpus striatum, viâ the ansa lenticularis, nucleus ruber, and rubro-spinal tract, to the anterior cornual cells. In what way impulses originate in the corpus striatum is immaterial—they may depend on stimuli from the optic thalamus by thalamo-striate fibres; in any case, the evidence for the efferent action of corpus striatum impulses on the final common path, by the route just mentioned, is not to be lightly set aside. I have said that this influence is one which steadies pyramidal innervation along the final common path. In the absence of this influence tremor is likely to occur, and, as a rule, with increase of pyramidal action so will the tremor increase. It is an action-tremor. The reader is referred to my monograph for a full discussion of the evidence associating tremor as well as hypertonicity of the skeletal muscles with defect of function of this internuncial system.

The accompanying diagram (fig. 26) indicates sufficiently, and in a graphic manner, the way in which I conceive the corpus striatum to act.

One or two questions remain for brief discussion. It may be asked, if this be the function assigned to the corpus striatum, and these the results of interference with that function, how is it I have been unable to obtain such symptoms in apes whose ansa lenticularis has been completely degenerated, or in whose corpus striatum large lesions have been placed? It may be said by way of response that the data mentioned above, in Section (2) of this chapter, will show how different are the anatomical relations and proportions of the pallium and corpus striatum in different animal species, and it will be understood, as has already been remarked, that the function of the latter structure in apes may not be identical with its function in man.[1] In fact the probability is that it is not identical. It should be borne in mind in this connexion that if the volume of the total encephalon be taken as 100, the proportionate volume of the basal ganglia is in man, 5; in the ape, 8; in the dog, 11; in the sheep, 14; and so on. That is to say, there are certainly structural differences in this matter between man and the ape. Again, there are undeniable physiological differences in the various animal groups, as far as the independent action of inferior and superior motor centres are concerned. Complete section of the cervical or upper dorsal cord in the frog does not diminish muscular tone in the limbs, according to Crocq [15]; in the dog there is momentary diminution of tone, which soon returns, but not quite to the same degree as before; in the ape, there is persistent and marked diminution of tone; in man, there is definite and complete abolition of tone. Analogous results are obtained when the motor area of the cortex is destroyed in these respective animals, as far as the region innervated by the destroyed cortical zone is concerned. Again, it is well known that the degree of recovery of movement after lesions destructive of the motor cortex in animals and in man varies considerably. After completely extirpating the hand area from the right hemisphere of a chimpanzee Grünbaum and Sherrington saw an immediate severe crossed brachioplegia, but it diminished rapidly, and in six weeks' time the animal had in large measure recovered the usefulness of the limb. In dogs and other animals lower in the scale the resulting paresis is even slighter and the recovery greater.

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[1] It should also be noted that I did not allow any of my animals to live longer than three weeks, while there is a possibility that longer time should elapse after the lesion before the onset of tremor could be expected.

In fact, the expression "motor centres" conveys very different meanings according as we speak of one or other animal group. As Mills [52] has said, in the rabbit, cat and dog, for instance, the motor centres of the cerebral cortex are not on the same functional plane. And this is equally true of higher mammals. There are differences in the *organization* of the various motor centres, moreover: in man, to take but one example, all movements are not equally readily abolished by cerebral disease, or equally readily restored. It is possible to remove the entire cerebrum of the pigeon, yet it is capable of flight when thrown into the air an hour later. On the day of the removal of the cerebral centres from the limbs, a rabbit will jump vigorously. A week after removal of the crucial motor area, a puppy will walk, run, scratch, &c., as before. Obviously it is not the same with the monkey, still less with man.

These facts are mentioned simply to show that man is much more dependent on his motor cortex than are the lower animals, and they suggest—what indeed a consideration of the facts of comparative anatomy has already emphasized—that corresponding differences in the importance of the corpus striatum for motility are only to be expected.

The matter may be put in another way. In all the vertebrates there are higher and lower motor centres; in all, the latter are constituted by collections of grey matter in the cord and medulla and pons; the former are constituted by the corpus striatum in the lowest vertebrates, and by the motor pallium in the superior grades. The assertion is that the degree of independent action of the lower motor centres is greater in the less highly developed than in the more highly developed groups of the vertebrate series; the relation of the corpus striatum to its lower motor centres is different from that of the rolandic cortex to its lower motor centres. The corpus striatum, phylogenetically speaking, has never been a "lower motor centre," and in the event of cortical defect of function the degree of movement possible will depend on the organization of the lower motor centres, of which the corpus striatum is not one. In spite of the general similarities between the brains of the ape and of man, we cannot assume that a lesion of the corpus striatum in the one will result in the same disturbance of motility as is found with an analogous lesion in the other.

We have seen that in birds there *may* be a vicarious functioning of the corpus striatum for the motor pallium. The question arises whether in man any compensation for pyramidal failure may be possible by extra-pyramidal routes. My own opinion is that this is extremely unlikely. We have neither anatomical nor physiological justification for such a hypothesis. The suggestion has been made by Probst [61] among others, that in the "Haubenbahnen" we have extrapyramidal paths capable of functioning for the pyramidal path. By these he means the tractus tecto-spinalis, rubro-spinalis, &c. They descend to the spinal cord from the mid-brain. But, in the first place, we have no anatomical knowledge of the way in which they might conceivably be reached from the motor cortex, except in so far as there is a fronto-rubral tract. Again, if compensation, of this kind be it noted, is possible, it should be met with constantly: this, however, is not the case. Permanent motor paralysis certainly occurs in man. As for the "centres" from which these descending "Haubenbahnen" arise, they are incapable, for anatomical reasons if for no other, of developing that capacity for complex and varied movement which would justify their being described as "lower motor centres."

The loose way of referring to "subcortical motor centres" in the basal ganglia and mid-brain is to be deprecated. We are using two different connotations of "motor centre" if we apply it both to the motor cortex and the nucleus ruber. The sole subcortical motor centres which exist are the columns of motor cells in the anterior cornua, with their bulbar and pontine homologues. There may be, and probably is, in man, a latent power of subsidiary development of adjacent (perhaps not necessarily adjacent) *cortical* areas and tracts to compensate to some extent for loss of pyramidal function; thus when a patient cannot write with his right hand, owing to a hemiplegia, he may learn to write with his left hand, or with his foot, or even with his nose he may indicate letters; in a case recorded by Bruce a completely paralysed patient affixed his "signature" to a document by holding the pen in his teeth and making appropriate movements with his head. Apart from this, however, a lesion of the pyramidal system in man entails permanent loss of certain movements—a state which does not appear to obtain in the ape. The degree to which the spinal cord is capable of automatic function has not yet been sufficiently investigated, so far as man is concerned, but it is known that in the lower animals—Goltz's [33] dog is a classical instance—the spinal cord achieves very much in the absence of the motor cortex. In that instance the corpus striatum, as well as the cortex, was removed [43]. Of old the Emperor Commodus decapitated his ostriches in the arena, round which they nevertheless continued to perambulate for a long time. It is probable that in man the subcortical, *i.e.* medullary, motor centres do not possess, or rather retain, that faculty of independent action so characteristic of creatures lower in the scale. But there is no vestige of evidence, I repeat, that in man the corpus striatum is capable of assuming a long-lost function and of acting vicariously for the motor pallium. Its true motor function has gone, never to return.

One final question remains. Admitting that the corpus striatum has no longer any motor activity comparable to that of the motor cortex or of the spinal cord, and that its motor function is one of steadying (I purposely avoid using the difficult word "inhibiting") innervation as it streams along the final common path, is there any evidence to suggest that the organ under discussion has developed in other ways, and that it may be associated with innervation of non-striped muscle fibre? Does it bear any relation to organic, visceral activity? Has it to do with a central representation of the sympathetic and autonomic systems?

Langelaan [42] has put forward the hypothesis that the corpus striatum, with the body of Luys and the substantia nigra, is the highest motor centre for non-striped muscle. A great deal of attention has at different times been devoted to a consideration of the view that in the corpus striatum is a heat-regulating centre; also a respiratory centre, a vasomotor centre, a blood-pressure and pulse-controlling centre, and so on. There are obvious difficulties in the way of accurately determining such functions by experiment, and the evidence hitherto adduced is far from convincing, besides being in some ways contradictory. The variety of animals operated on is also a very important complicating factor.[1] In my own experiments no evidence was obtained of any disturbance of respiration from stimulation or destruction of the putamen or globus pallidus in apes. And, further, the question must always remain, assuming any of these functions for the sake of argument, how are they carried out? Until we have clear anatomical proof of the connexion of the corpus

[1] It would make this paper much too long if one were to attempt anything like a complete résumé of these various investigations, the original descriptions of a large number of which have been perused. The unsatisfactory nature of much of the work has been clearly exposed by v. Bechterew [6], to whose chapters on the subject the reader is referred. Very briefly, the following are his main conclusions. (1) The corpus striatum (nucleus candatus) is not a centre for respiration; (2) nor for the vocal cords; (3) it has no influence on movements of the stomach and alimentary canal; (4) it has no connexion with the urinary bladder; (5) nor with the organs of sex; (6) it may have some association with the heart and blood-vessels by the vasomotor system; but similar experimental data are obtained from the optic thalamus; (7) it may have some connexion with the maintenance of body temperature, but how this is effected is quite obscure.

striatum with recognized bulbar centres, by direct or even intercalated neuronic communication, we cannot get any further in such matters. Such anatomical proof, as far as my knowledge goes, is not yet forthcoming.

BIBLIOGRAPHY.

[1] Ariëns Kappers. "Die Phylogenese des Rhinencephalons, des Corpus striatum und der Vorderhirnkommissuren," *Folia Neuro-biologica*, Januar, 1908, Bd. i, Nr. 2, S. 173.

[2] *Idem.* "Weitere Mitteilungen über die Phylogenese des Corpus striatum und des Thalamus," *Anat. Anzeig.*, 1908, Bd. xxxiii, Nr. 13 und 14, S. 321.

[3] Baginsky and Lehmann. "Zur Function des Corpus striatum (Nucleus caudatus)," *Virchow's Archiv*, 1886, Bd. cvi, H. 2, S. 258.

[4] Beaunis. "Note sur l'application des injections interstitielles à l'étude des fonctions des centres nerveux," *Gaz. méd. de Paris*, 1872, Nos. 30, 31 and 33, pp. 358, 371, 396.

[5] v. Bechterew. "Die Leitungsbahnen im Gehirn und Rückenmark," zweite Auflage, Leipzig, 1899.

[6] *Idem.* "Die Funktionen der Nervencentra," 1909, Bd. ii, S. 1224 *et seq.*

[7] Bianchi. "Sul significato della eccitazione elettrica della zona motrice corticale," *Nov. Med. Chirurgico*, 1880, fasc. 8. (*See also* critical digest in *Brain*, 1881-2, vol. iv, p. 233.)

[8] Braun. "Ueber Beiträge zur Frage über die elektrische Erregbarkeit des Grosshirns," *Eckhard's Beiträge zur Anat. u. Physiol.*, 1876, Bd. vii, S. 127.

[9] Brissaud. "Paralysie pseudo-bulbaire cérébrale," "Leçons sur les maladies nerveuses," 2nd ser., Paris, 1899, p. 295.

[10] Broadbent. "An Attempt to remove the Difficulties attending the Application of Dr. Carpenter's Theory of the Function of the Sensori-motor Ganglia to the Common Form of Hemiplegia," *Brit. and For. Med.-Chir. Rev.*, April, 1866, p. 468.

[11] Budge. "On the Dependence of the Intestines' Motions on the Central Organs of the Nervous System," *Lond. Med. Gaz.*, 1839-40, vol. i, p. 957.

[12] Burdach. "Vom Baue und Leben des Gehirns," 1819.

[13] Cajal. "Histologie du Système nerveux de l'homme et des vertébrés," Paris, 1909.

[14] Charcot. "Leçons sur les localisations dans les maladies du cerveau," Paris, 1876.

[15] Crocq. "Le mécanisme du tonus musculaire, des réflexes et de la contracture," *L'Encéphale*, 14 fevrier, 1914, p. 147.

[16] Darkschewitsch and Pribytkow. "Ueber die Fasersysteme am Boden des dritten Hirnventrikels," *Neurol. Centralbl.*, 1891, S. 417.

[17] Dejerine. "Anatomie des centres nerveux," Paris, 1901.

[18] Edinger. "On the Importance of the Corpus Striatum and the Basal Fore-brain Bundle," *Journ. Nerv. and Ment. Dis.*, 1887, vol. xiv, p. 674.

[19] *Idem.* "Die Faserung aus dem Stammganglion Corpus Striatum," *Verhandl. der Anat. Gesellsch.*, Strassburg, May, 1894, S. 53.

[20] *Idem.* "Sur l'anatomie comparée du corps strié (cerveau des oiseaux)," *Comptes-rendus de l'Assoc. des Anat.*, Liège, 1903, p. 187.

[21] *Idem.* "Vorlesungen über den Bau der nervösen Centralorgane des Menschen und der Tiere," 7th ed., Leipzig, 1911.

[22] Ferrier. "Experimental Researches in Cerebral Physiology and Pathology," *West Riding Lunatic Asylum Medical Reports*, 1873, vol. iii, p. 30.

[23] *Idem.* "The Functions of the Brain," London, 1876.

[24] Flechsig. "Weitere Beobachtungen über den Faserverlauf innerhalb der nervösen Centralorgane," *Centralbl. f. d. med. Wissensch.*, 1877, Bd. xv, S. 35.

[25] *Idem.* "Zur Anatomie und Entwickelungsgeschichte der Leitungsbahnen im Grosshirn des Menschen," *Arch. f. Anat. u. Physiol.*, Anat. Abt., 1881, S. 12.

[26] Flourens. "Recherches expérimentales sur les propriétés et les fonctions du système nerveux dans les animaux vertébrés," 2nd ed., Paris, 1842.

[27] Forel. "Untersuchungen über die Haubenregion und ihre oberen Verkämpfungen im Gehirne des Menschen und einiger Säugetiere," *Arch. f. Psychiat.*, 1877, Bd. vii, S. 393.

[28] Fournié. "Recherches expérimentales sur le fonctionnement du cerveau," *Comptes-rendus de l'Acad. des Sc.*, 1878, vol. lxxv, p. 1194.

[29] François-Franck and Pitres. "Sur l'inexcitabilité du noyau intraventriculaire du corps strié et sur l'excitabilité de la capsule interne," *Comptes-rendus, Soc. de Biol. de Paris*, 1878 (pub. 1880), p. 34.

[30] Fraser. "An Experimental Research into the Relations of the Posterior Longitudinal Bundle and Deiters's Nucleus," *Journ. Physiol.*, 1901, December 23, vol. xxvii, p. 372.

[31] Van Gehuchten. "Anatomie du système nerveux de l'homme," Louvain, 1900.

[32] Gliky. "Ueber die Wege auf denen die durch elektrische Reizung der Grosshirnrinde erregten motorischen Thätigkeiten durch das Gehirn hindurch fortgeleitet werden," *Eckhard's Beiträge zur Anat. u. Physiol.*, 1876, Bd. vii, S. 177.

[33] Goltz. "Der Hund ohne Grosshirn," *Pflüger's Archiv*, 1892, Bd. li, S. 570.

[34] Grünbaum and Sherrington. *See* Sherrington.

[35] Grünstein. "Zur Frage von den Leitungsbahnen des Corpus striatum," *Neurol. Centralbl.*, 1911, Bd. xxx, S. 659.

[36] Halipré. "La paralysie pseudo-bulbaire d'origine cérébrale," Paris, 1894.

[37] Hitzig. "Untersuchungen über das Gehirn," *Centralbl. f. d. med. Wissensch.*, 1874, Bd. xii, S. 548.

[38] Horsley and Clarke. "The Structure and Functions of the Cerebellum examined by a New Method," *Brain*, 1908, vol. xxxi, p. 45.

[39] Johansen. "Ein experimenteller Beitrag zur Kenntniss der Ursprungstätte der epileptischen Anfälle," Inaug. Dissert., Dorpat, 1885.

[40] Johnston. "The Nervous System of Vertebrates," London, 1907.

[41] De Lange. "L'évolution phylogénétique du corps strié," *Le Névraxe*, 1913, vol. xiv, p. 105.

[42] Langelaan. Cited by de Vries.

[43] Langley and Grünbaum. "On the Degeneration resulting from Removal of the Cerebral Cortex and Corpora Striata in the Dog," *Journ. Physiol.*, 1890, vol. xi, p. 606.

[44] Lo Monaco and Bellanova. "Contribution expérimentale à la physiologie du noyau caudé," *Gaz. hebdom. de méd.*, 1902, November 27, p. 1118.

[45] Longet. "Anatomie et physiologie du système nerveux," Paris, 1842.

[46] Luciani and Tamburini. "Ricerche sperimentali sulle funzioni dell cervello," *Riv. sper. di fren.*, 1878, vol. iv, p. 69.

[47] Lussana and Lemoigne. "Sur les centres moteurs encéphaliques," *Arch. de Physiol.*, 1877, p. 119.

[48] McKendrick. "Observations and Experiments on the Corpora Striata and Cerebral Hemispheres of Pigeons," *Trans. Roy. Soc. Edin.*, 1873.

[49] Magendie. "Leçons sur les fonctions et les maladies du système nerveux," Paris, 1841.

[50] Mahaim. "Ein Fall von sekundärer Erkrankung des Thalamus opticus und der Regio subthalamica," *Arch. f. Psychiat.*, 1893, Bd. xxv, S. 343.

[51] Marinesco. "Des connexions du corps strié avec le lobe frontal," *Comptes-rendus, Soc. de Biol. de Paris*, 1895, February 2, p. 77.

[52] Mills. "The Functional Value of Cortical Cerebral Motor Centres in Different Animals," *New York Med. Journ.*, 1896, October 17, p. 513.

[53] Mingazzini. "Das Linsenkernsyndrom," *Zeitschr. f. d. ges. Neurol. u. Psychiat.*, 1911, Bd. viii, H. i, S. 85.

[54] Minor. "Signification et rôle du corps strié," Inaug. Dissert., Moscow, 1889.

[55] v. Monakow. "Experimentelle u. pathologisch-anatomische Untersuchungen über die Haubenregion, den Sehhügel und die Regio subthalamica," *Arch. f. Psychiat.*, 1895, Bd. xxvii, S. 1.

[56] *Idem.* "Gehirnpathologie," zweite Auflage, Wien, 1905.

[57] MONAKOW. "Der rote Kern, die Haube und die Regio hypothalamica," *Arbeiten a. d. hirn-anat. Institut in Zürich*, 1910, H. 3, S. 53.

[58] MUNK. "Ueber die Funktionen der Corpora striata," *Comptes-rendus, Congrès internat. Kopenhagen*, 1884, Section de Physiologie, t. i, p. 57.

[59] NOTHNAGEL. "Experimentelle Untersuchungen über die Funktionen des Gehirns," *Virchow's Archiv*, 1873, Bd. lvii, S. 184.

[60] OBERSTEINER. "Anleitung beim Studieren des Baues der nervösen Centralorgane," Leipzig and Wien, 1888.

[61] PROBST. "Ueber vom Vierhügel, von der Brücke und vom Kleinhirn absteigende Bahnen," *Deutsche Zeitschr. f. Nervenheilk.*, 1899, Bd. xv, S. 192.

[62] *Idem.* "Ueber die Rinden-Sehhügelfasern, die Schweifkernfaserung, usw.," *Archiv f. Anat. u. Physiol.*, Anat. Abt., 1903, S. 146.

[63] *Idem.* "Zur Kenntniss der Grosshirnfaserung und der cerebralen Hemiplegie," *Sitzungsb. d. kaiserlich. Akad. d. Wissensch.*, Wien, 1903, Bd. 112, Abt. iii, S. 581.

[64] *Idem.* "Ueber die zentralen Sinnesbahnen und die Sinneszentrum des menschlichen Gehirns," *ibid.*, Wien, 1906, Bd. cxv, Abt. iii, S. 103.

[65] PRUS. "Ueber die fei elektrischer Reizung des Corpus striatum und des Thalamus opticus auftretenden Erscheinungen," *Wien. klin. Wochenschr.*, 1899, November 30, S. 1199.

[66] ROSS. "A Treatise on the Diseases of the Nervous System," 2nd ed., London, 1883

[67] SACHS. "On the Structure and Functional Relations of the Optic Thalamus," *Brain*, August, 1909, vol. xxxii, part ii, p. 95.

[68] SANDERSON, BURDON. "Note on the Excitation of the Surface of the Cerebral Hemispheres by Induced Currents," *Proc. Roy. Soc.*, 1873-4, vol. xxii, p. 368.

[69] SCHIFF. "Beitrag zur Kenntniss des motorischen Einflusses der im Sehhügel vereinigten Gebilde," *Arch. f. physiol. Heilk.*, 1846, Bd. v, S. 667.

[70] SCHÜLLER. "Reizversuche am Nucleus caudatus des Hundes," *Pflüger's Archiv*, 1902, Bd. xci, S. 477.

[71] SHERRINGTON. "The Integrative Action of the Nervous System," London, 1906.

[72] SMITH, ELLIOT. "Some Problems relating to the Evolution of the Brain," *Lancet*, 1910, January 1, 15 and 22, pp. 1, 147, 221.

[73] STIEDA. "Ueber die Bedeutung des Nucleus caudatus," Dissert., St. Petersburg, 1903. (Cited by v. Bechterew.)

[74] SWEDENBORG. "Oeconomia Regni Animalis," 1740. (*See also* "Swedenborg on the Cerebral Cortex as the Seat of Psychical Activity," by Professor Ramström, *Trans. Internat. Swedenborg Congress*, London, 1910, p. 56.)

[75] TARASEWITSCH. "Zum Studieren der mit dem Thalamus opticus und Nucleus lenticularis in Zusammenhang stehenden Faserzüge," *Arbeit. a. d. neur. Inst. a. d. Wien. Universität*, 1902, Bd. xi, S. 251.

[76] TSCHERMAK. "Notiz betreffs des Rindenfeldes der Hinterstrangbahnen," *Neurol. Centralbl.*, 1898, Bd. xvii, S. 159.

[77] VAN VALKENBURG. "Experimental and Pathologico-anatomical Researches on the Corpus Callosum," *Brain*, 1913, vol. xxxvi, part ii, p. 119.

[78] DE VRIES. "Das Corpus striatum der Säugetiere," *Anat. Anzeig.*, 1910, Bd. xxxvii, Nos. 15 u. 16, S. 385.

[79] WERNICKE. "Zur Gehirnanatomie," *Arch. f. Anat. u. Physiol.*, Phys. Abt., 1880, S. 162.

[80] WERTHEIMER and LEPAGE. "Sur les mouvements des membres produits par l'excitation de l'hémisphere cérébral du côté correspondant," *Arch. de Physiol.*, 1897, p. 168.

[81] WIETING. "Zur Physiologie der Infrakortikalen Ganglien," Inaug. Dissert., Dorpat, 1891. (Cited by v. Bechterew.)

[82] WILSON, S. A. K. "Progressive Lenticular Degeneration," *Brain*, 1912, vol. xxxiv, p. 295.

[83] ZIEHEN. "Zur Physiologie der infrakortikalen Ganglien und über ihre Beziehungen zum epileptischen Anfall," *Arch. f. Psychiat.*, 1890, Bd. xxi, S. 863.

ON APHASIA DUE TO ATROPHY OF THE CEREBRAL CONVOLUTIONS.

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SCARCELY ten years have elapsed since attention was drawn, first by Pick and subsequently by Dejerine and myself, to certain cases of aphasia which, as was proved by autopsy, were not caused by tumours or other diseases of the speech-zone, but were due to more or less severe atrophy of the respective convolutions.

Although the preceding observations have since been partially confirmed by other writers, nevertheless the literature dealing with this subject is still very scanty, and often consists of accounts of incomplete researches. For this reason, I have decided to publish the details of the following case, which I studied both during life and *post mortem* at the lunatic asylum in Rome.

Pio Marini, aged 59, a gilder. The patient, from his condition, is unable to give any information. He has never suffered from any infectious disease, or from syphilis, and has been moderate in the use of wine. About two years previously (1907), the first symptoms of the disease began to show themselves rapidly. These consisted in a tendency to impulsive actions, as well as in a difficulty in speaking and in understanding what was said. Those around the patient noticed that he gave the most curious names to the commonest objects (paraphasia); and that when his intimates did not understand him, and persevered in trying to ascertain his wishes, Marini could not comprehend their questions and broke out into threats and accesses of rage. The symptoms continued slowly and gradually to increase, without any signs of a stroke.

This state of affairs obliged the patient's relatives to send him to the lunatic asylum on March 1, 1909.

The patient's condition, March 10, 1909.—The eye movements, as far as they can be tested, are normal. In showing the teeth, the right upper lip becomes tremulous; the tongue can be fully protruded, and is slightly turned towards the left. The upper and lower limbs are able to perform all the usual active and passive movements, but, in producing the latter, the amount of resistance encountered is somewhat greater than the normal. The tendons and periosteal reflexes of the upper limbs, and especially those of the lower limbs (patellar and Achilles tendons) are exaggerated. There is sometimes very evident foot clonus of the left side; the plantar reflexes give a flexor response. The abdominal reflexes are greatly exaggerated. A general hypalgesia is present. Speedy dermographia is evident.

Condition, March 12, 1909.—The patient remains quiet. At first he used to rave somewhat, and often called for a certain Don Antonio, who, according to him, ought to take him home; then he became calm, and showed himself indifferent. Echolalia is often noticed.

Examination of the patient's speech.—When questioned, the patient replies correctly only when asked his christian name and his surname. If other simple questions are put to him, he either repeats them (echolalia, or perseveration), or says: "Don Antonio"; "I do not know." He carries out verbal commands, provided they involve more or less common movements, with exactitude and rapidity; when, however, it is a question of obeying orders which are a little more complicated, he always replies "Don Antonio," and does not execute (does not understand) the order. He repeats words exactly. On being shown objects, and asked to name them, he succeeds at first (spoon, glass) and then replies as follows:—

Q.	A.
What is this called? (a bottle).	Don Antonio.
,, ,, (an inkstand).	Marini Pio.
,, ,, (a pen).	Marini Pio, gilder; then, *I do not know;* then, *a paint brush.*
,, ,, (nose).	Nose (after touching it).
,, ,, (ear).	Ear (*idem*).
,, ,, (lips).	Chin.
,, ,, (a watch).	I do not know.

When invited to read, he often repeats: "Marini Pio," or "Don Antonio." Sometimes, on beginning to read, the patient reads two or three words correctly, and afterwards reads some words in a quite mutilated manner, and then stops, puts down the book, and tries to induce the examiner to allow him to do something else.

Written to dictation:—

Marini Pio.	Marini Pio.
Manicomio. Roma. Roma.	The patient always writes Marini Pio.

Copied.—The sentence to be copied ran as follows: "Se avete dei dubbi sulla campagna elettorale del 'Messaggero' (if you have any doubts as to the electoral campaign of the 'Messaggero')." He wrote "Marini Pio."

Condition, August 5, 1909 :—

Examination of Speech. Q.	*Perception of Commands.* A.
What is your name ?	Pio Marini.
Shut your eyes.	He obeys.
Open your mouth.	The patient does not open his mouth, but closes his eyes.
Stand up.	He obeys.
Sit down.	He obeys.
Raise your right arm.	The patient gets up and raises his left arm.
Get up, and go to the door.	The patient gets up, but does not go to the door.
Take the inkstand.	The patient does not obey the order.

The patient thus understands part only of the commands. He often repeats the last words of the orders without understanding them (echolalia automatica), e.g., Stand up, he repeats: "Stand up" (and does not do so), Go to the window; he says: "Go to the window" (but does not obey). At other times he persists in using the same words; thus when shown different objects such as a pencil, a glass, spectacles, and asked their names, he always says: "Don Antonio."

Condition, February 12, 1910 :—

Examination in the Comprehension of Speech. Q.	*Perception of Commands.* A.
Shut your eyes.	He obeys.
Put out your tongue.	He obeys.
Stand up.	The patient does not obey, but says: "Don Antonio."
Give me your hand.	The patient raises both hands, but does not obey.
Shut the door.	The patient shuts his eyes.
Touch your ear.	The patient does not obey, and exclaims "Don Antonio."
Put on your cap.	He repeats : "Put on your cap," but does not do so.

Repetition of Words.

Q.	A.
Roma.	Roma.
Papa.	Papa.
Angelo (angel).	Angelo.
Repubblica (republic).	Repubblica.

Q.	A.
Uccello (bird).	Uccello.
Napoli (Naples).	Napoli.
Il mare è immenso (the sea is vast).	Immenso.
Il cielo è bello (the sky is beautiful).	The patient first repeats "il cielo," and, on the command being repeated, replies: "è bello."
La campagna è bella (the country is beautiful).	E bella.
Repubblica popolare (popular republic)	Popolare.
La casa è grande (the house is large).	This the patient does not repeat.
Circoscrizione (circumscription).	The patient repeats the word with some clear dysarthric disturbances.
Circondariale.	Circondariale.
Artiglieria (artillery).	Artiglieria? I do not know the word.
Circoncisione (circumcision).	He does not repeat the word.

When several objects are placed before the patient, and he is requested to carry out an order, the results are as follows:—

Q.	A.
Take the watch.	The patient obeys.
Take two soldi (two five centesimi pieces).	He does not do so.
Take the keys.	The patient does not obey, but exclaims "Don Antonio."
Take the scissors.	Idem.
Take the book.	Idem.
Take the inkstand.	Idem.
Take the bottle.	Idem.
Take the hat.	Idem.
Take the handkerchief.	He takes a ten-centisimi piece.

When different objects are shown to the patient, and he is asked to name them separately, the results are as follows:—

Object shown.	A.
A watch.	A watch.
A pair of scissors.	A pair of spectacles.
On making him take them in his hand.	I do not know.
A soldo (making him feel it).	I do not know. Don Antonio.
A pair of spectacles.	Don Antonio.
A bottle.	Don Antonio

The patient thus showed signs of partial sensory aphasia, amnesia verborum, verbal paraphasia, paralexia, and almost complete agraphia.

Condition, October 18, 1910.—The patient is always taciturn; he spends the whole day in walking aimlessly about in a state of complete apathy, and takes no interest in anything around him. He cannot find his bed, the water-closet, does not know the hours of the meals, and at meal-time has to be put in his right place. He often eats with his hands, but when convenient he also uses a spoon. If a plate of soup is placed before him, the patient begins to eat with his hands, then he takes up his spoon properly, but nevertheless he eats now with his spoon, and now with his hands. He is not able to dress or undress himself properly; in dressing himself he puts on his trousers, and also his vest, and draws his shirt over the latter and buttons them correctly; then he takes his socks, and goes in this condition out of the dormitory to the first door he comes across. Sometimes when dressing himself he tries instead to take off his vest.

His spontaneous speech is reduced to the monotonous repetition of the words, "Don Antonio." When asked to read the sentence, "Senza pieta" (without pity), he reads "Aprile 30." When the request is repeated, he reads: "Piri piri, pi." When asked to read "Concorso ippico," he reads "Don Antonio." The patient is unable to read any easy written sentence, however short. He is also incapable of reading or recognizing single letters and numbers, or even a single figure. When asked to write out of his head, or from dictation, or to copy, he merely makes the following hieroglyphic, "m m."

Comprehension of Questions.

Q.	A.
How old are you?	Don Antonio.
What is your name?	No reply.
To what country do you belong?	No reply.
What is your father's name?	No reply.

Repetition: His spontaneous speech is reduced to pronouncing the words, "Don Antonio"; he retains the capacity of repeating these words, although with decided dysarthric troubles; word-blindness and agraphia are complete, and word deafness is almost complete.

Voluntary movements of the face, the tongue and limbs, together with the tendon reflexes, were in the same condition as at the time of the preceding examinations.

The patient has a good perception of light when it comes from the right or left, but shows a certain fear if the light approaches too near his eyes.

Condition, October 23, 1910.—In the afternoon the patient suddenly began to run of his own accord, and fell down, producing abrasions of the skin on the right side of his face. As a rule, he only walks aimlessly about the garden, he does not recognize the refectory, the water-closet, or the dormitory, and always needs assistance in finding his own bed. In dressing, he is always able to put on his vest and shirt properly, but is unable to get on his coat, unless the nurse puts it on his shoulders, when he manages quite well. Often, after putting on one shoe and sock, he goes out of the room and begins to walk about, carrying the other sock in his hand. As a rule, he does not succeed in putting on both socks without the assistance of the nurse. Almost every morning, while sitting on his bed, he draws his socks over his hands, and then puts his hands into his shoes, then, however, following the suggestions and indications of the nurse, he finishes by putting on his socks and shoes properly. He eats, for the most part, with his hands, but when necessary he

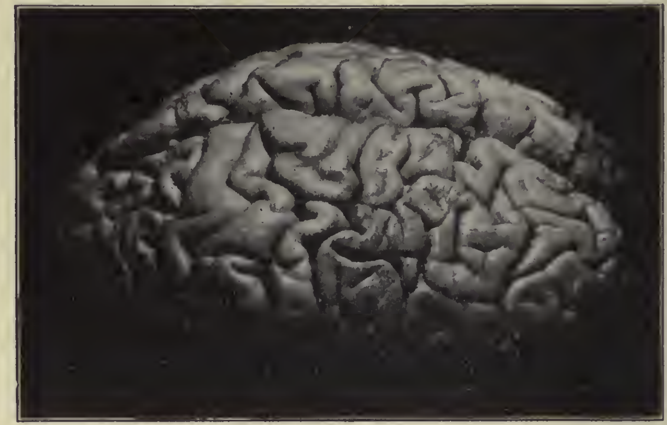

Fig. 1.—Photograph of the brain seen obliquely from above. Note on the right, the contrast between the enormous atrophy of the convolutions of the prefrontal lobe, and the normal volume of the rolandic convolutions.

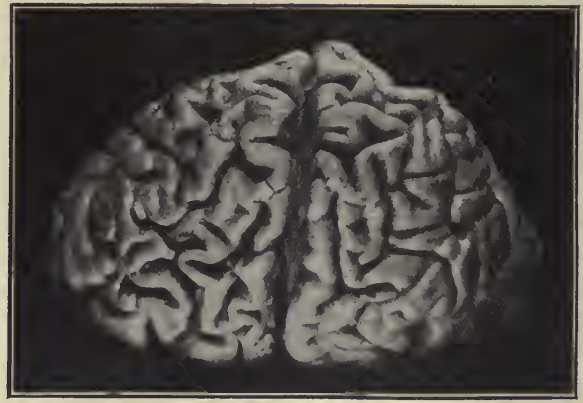

Fig. 2.—Photograph of the prefrontal lobes of the brain, seen from above. Note the enormous extent of the atrophy of the corresponding convolutions.

manages his spoon well. At night he undresses himself properly and folds up his clothes neatly.

The late appearance and slow progress of the symptoms of aphasia, the absence of strokes or any focal symptoms, together with the ever-increasing dementia, led me to conclude that the patient was developing progressive atrophy of the cerebral convolutions, to which must be attributed the increasing speech defects. This diagnosis was confirmed by his death, which occurred on December 15, 1910.

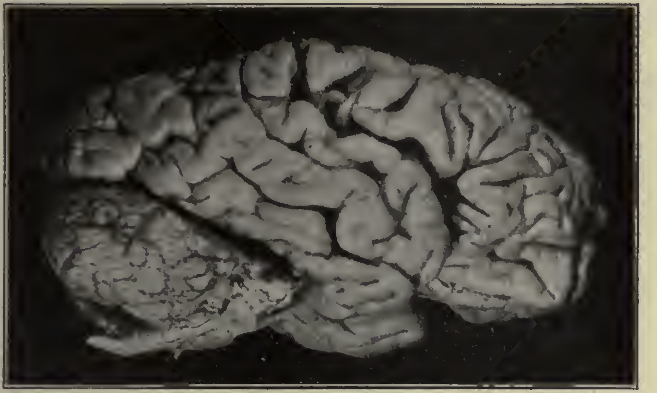

Fig. 3.—Photograph of the right cerebral hemisphere of the brain of the same patient. Note the conspicuous atrophy of the pars opercularis of F^3 and of the middle and posterior portion of T^1.

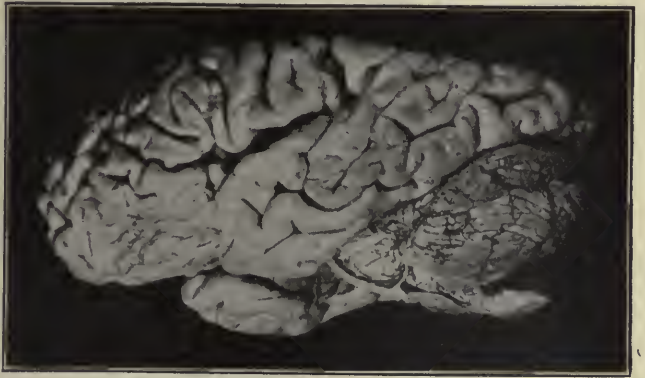

Fig. 4.—Photograph of the left cerebral hemisphere of the same patient. Note the serious atrophy of the pars opercularis of F^3 and of the middle portion of T^1.

Autopsy.—There is nothing amiss with the dura mater. The pia mater is normal and easily removed from the cerebral convolutions.

In the left hemisphere the frontal sagittal convolutions, especially the first and second, the pars orbitalis and triangularis of the third frontal convolution have noticeably decreased in volume (fig. 1), and scarcely attain half of their normal size; they seem of an almost fibrous consistency to the touch. The median and posterior parts of T^1 and T^2, and especially the gyrus angularis, are somewhat diminished (figs. 1 and 4). The corresponding sulci are enormously enlarged. In the right hemisphere the præ-frontal (fig. 2) and temporal convolutions are much reduced, although to a considerably less degree than is the case with those on the left (figs. 2 and 3). The median portion of T^1 is almost as much reduced as that of the corresponding convolution on the left side. In the zones where the convolutions are atrophied, the pia mater is raised here and there into little cysts containing a clear, serous liquid.

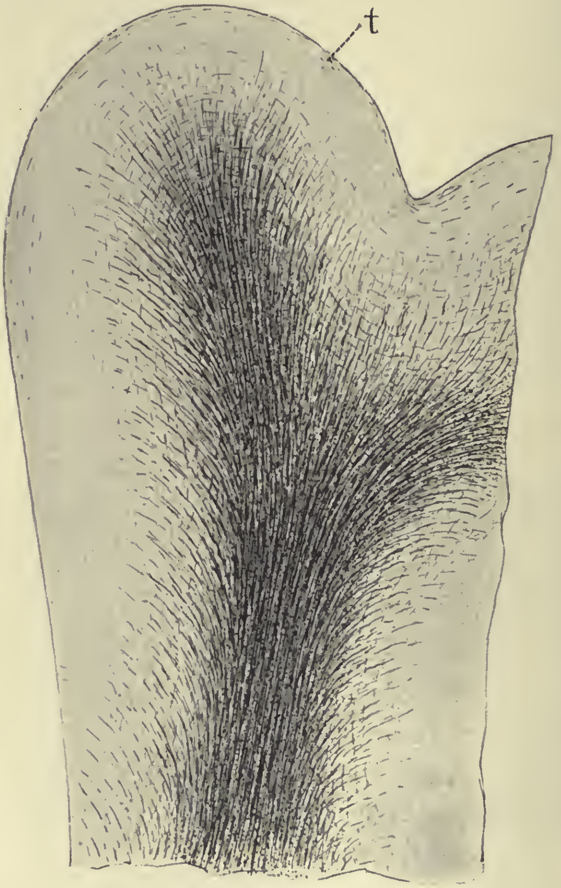

FIG. 5.—Section of the cortex of the left T^1. Stained with Pal's hæmatoxylin; *t*, tangential fibres. A very slight rarefaction of the fibres of the medullary axis is seen, the transverse fibres of the supraradial plexus are here and there slightly rarefied.

For the purpose of studying the condition of the cells, and the nerve-fibres of the cortex of the atrophied convolutions, and especially of those belonging to the acoustic and motor word spheres, I examined at measured points on the right and left, the pars opercularis of F^3 and the passage zone of the latter with the lower extremity of gyrus præcentralis and the median point of T^1. All these were stained either with Weigert-Pal's hæmatoxylin, or with hæmatoxylin-eosin.

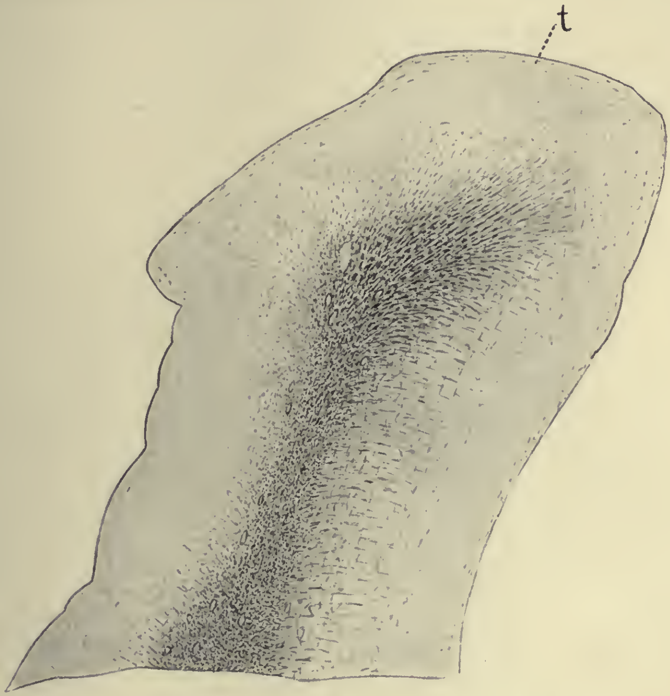

FIG. 6.—Section of the cortex of the middle portion of the pars opercularis of the left F^3 (staining as above). Note the almost complete disappearance of the tangential fibres (*t*) and of most of the fibres taking part in the formation of the infra- and supraradial plexuses. In one part of the section (on the left of the figure) the disappearance of the medullated fibres is so nearly complete, that scarcely any traces of them are visible. The fibres of the medullary axis are so rarefied and degenerate that even in the most successful preparations they are conspicuous from their very pale colour.

In sections cut at the level of the zone of passage between the pars opercularis of the left F^3 and the lower extremity of the gyrus præcentralis (fig. 11), the nerve-fibres composing the medullary axis are very scarce, many are very thin and dilated from time to time in such a manner as to have an actual moniliform structure. The radial bundles taking part in the formation of the infra- and supraradial plexuses are attenuated, and the nerve-fibres accompanying them are broken and dilated; some of the transverse fibres have disappeared, almost all that remain are broken and dilated; very rarely the tangential fibres are replaced by a few swollen fibrils.

In the sections of the same zone stained with hæmatoxylin-eosin, the nerve-cells of all the strata show, to a greater extent than in the other convolutions examined, the alterations already described, the disappearance of a considerable number of these elements being especially noticeable (fig. 12, and fig. 9, *a*, *b*, *c*, *d*).

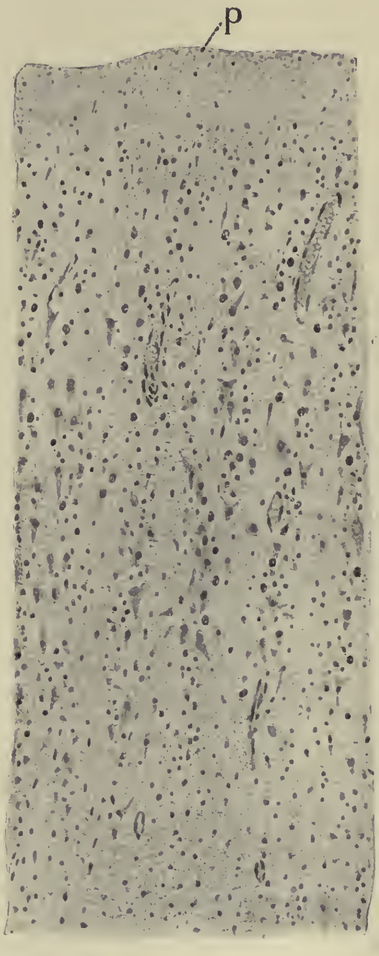

FIG. 7.—Section of cortex of the pars opercul of the left F^3 (stained with hæmatoxylin-eosin. Enlargement objective 4, ocular 2 Leitz); p, pia mater. A good number of the nerve-cells are present, and to much larger extent than in T^1; further, also here, there are but few which have kept their pyramidal form.

In sections cut on the level of the median part of the left pars opercularis of F^3 (fig. 6), the alterations of the medullary nerve-fibres described in the preceding sections are much more conspicuous. The fibres constituting the medullary axis, especially towards the dorsal (apical) half, are almost all broken during their course in such a manner that they are replaced by a number of little masses and fragments (of myelin) which are arranged without any order (fig. 8). In the same way, the transverse fibres, and also the radial fibres making up the two plexuses, have disappeared in much larger numbers. The tangential fibres are reduced to a few irregular fragments occurring here and there. Here we observe the same alterations of the nerve-cells as in T^1. The number of those preserved, however, is relatively larger (fig. 7, and fig. 9, *c*, *d*).

In frontal sections of the cortex of the median part of the left T^1 there are, in the medullary axis of the Pal preparations, numerous small bundles of well-preserved fibres (fig. 5), though here and there a fair number of degenerate medullated fibres occur, and small masses and drops of myelin. Also in the infra- and supraradial plexuses a good number of fibres have been preserved;

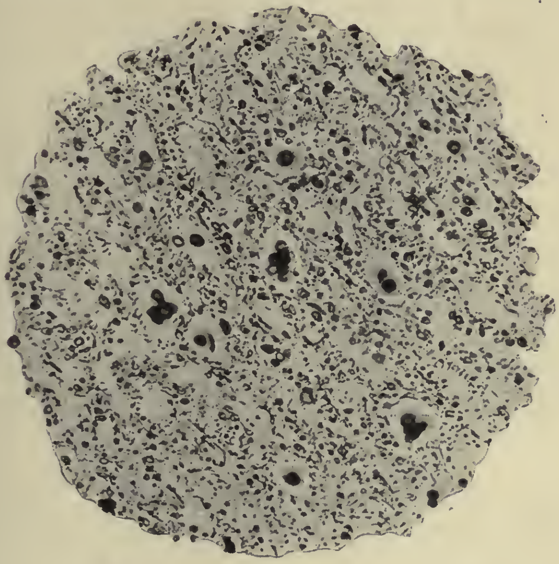

FIG. 8.—Segment of the medullary axis of the pars opercularis of the left F^3. Much enlarged. (Enlargement, objective 6·7, ocular 4 compens., Leitz.) In the place of the radial nerve-fibres running longitudinally are seen numerous little blocks of myelin, which are more or less dilated, and separated from one another by large clear spaces.

nearly all of these have, however, a moniliform structure owing to their having become dilated during their course. The tangential fibres are, to a great extent, preserved. In the hæmatoxylin-eosin preparations the following facts are observed; a considerable number of nerve-cells are seen to have disappeared, (fig. 10), and in almost a uniform manner in all the strata. In those which have still been preserved are clearly seen the nucleus with its network and nucleolus, in many the cytoplasm is almost completely filled with granules of a yellow pigment; in others the cytoplasm has in a great measure disappeared and only stains slightly (fig. 9, *e*, *f*). Thus, not a few of the pyramidal cells seem as if truncated, while in others the surrounding protoplasm has completely disappeared, and it is not always easy to distinguish the nucleus of the nerve-cell from the nuclei of the glia. The fibres and the cells of the glia are normal in number, only on the periphery of the cortex of the said convolutions are the bundles similar in their thickness and shape to those described and figured by Franceschi. Thus there is not always a correspondence between the changes in the nerve-cells, and those which have taken place in the medullary fibres, and in fact, while in the pars opercularis of the left F^3, the changes in the fibres are very great, those in the nerve-cells are relatively little noticeable. On the other hand, in the passage zone between the left F^3 and the gyrus præcentralis, the nerve-cells present extremely noticeable alterations, while the medullary nerve-fibres, though certainly changed, are altered to a much slighter extent.

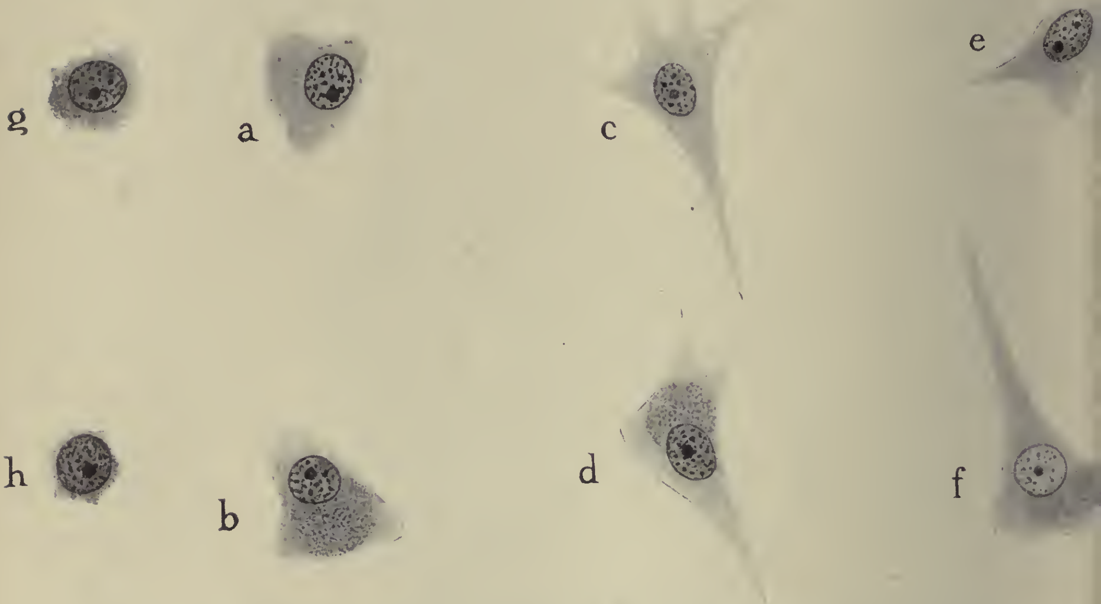

FIG 9 —Types of nerve-cells of the cortex of the convolutions belonging to the motor word and to the auditory speech zones of the left side. Stained with hæmatoxylin eosin. (Enlargement, Leitz, ocular, compens. 4, objective 1½ min.). *a* and *b* are nerve-cells belonging to the cortex of the passage zone between the pars opercularis of left F^3 and the gyrus præcentralis, in which the cytoplasm has in part disappeared; *b*, nerve-cells (pyramidal), in which the cytoplasm is in a great measure invaded by granules of yellow pigment; *g* and *h* are nerve-cells belonging to the same convolution, the cytoplasm has almost completely disappeared; *c* and *d*, pyramidal nerve-cells from the cortex of the pars opercularis of the left F^3; in *c*, the cytoplasm is slightly coloured; in *d*, the yellow pigment occupies a great part of the latter: *e* and *f*, nerve-cells belonging to the cortex of the left T^1; in *e* the cytoplasm has in part disappeared, and the prolongations appear as if truncated; in *f* the cytoplasm is, to a large degree, invaded by the yellow pigment.

In the right T^1 there is no appreciable reduction of the nerve-fibres of the medullary axis, nor in those of the supra- and infraradial plexuses; the tangential fibres are also but little reduced, although fairly numerous varicose dilatations of the latter occur occasionally.

In sections at the level of the passage zone of the pars opercularis of the right F^3 to the adjacent part of the gyrus præcentralis, the medullary nerve-fibres appear to be well preserved, only some rare varicose swellings are seen in the tangential fibres, and in some of the vertical fibres of the infra- and supraradial plexuses.

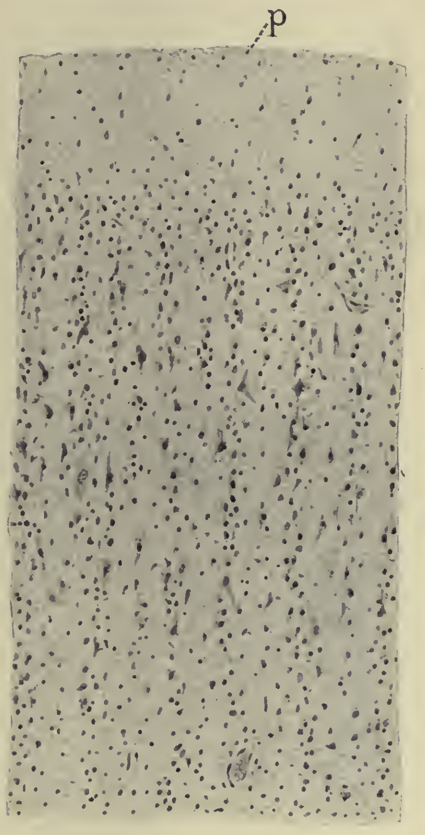

FIG. 10.—Section of the cortex of the left T^1 (stained with hæmatoxylin-eosin, enlargement objective 4, ocular 2, Leitz). Note the disappearance of many nerve-cells of the different strata of the cortex; the nerve-cells, especially the pyramidal ones, have to some extent lost their characteristic shape, owing to the loss of a considerable portion of the cytoplasm.

In the pars opercularis of the right F^3 (fig. 13), the changes are greater than in the other two zones, many of the tangential fibres have disappeared, while in these, and also in the transverse fibres, numerous varicose swellings occur. In the fibres of the medullary axis the disappearance of some fibres is noticeable.

In the nerve-cells of the right T^1 most of the cytoplasm has disappeared, and a few only of the cells are missing, although a larger number have disappeared in the sections of the passage zone from the right F^3 to the gyrus præcentralis, and still more in the pars opercularis of the right F^3.

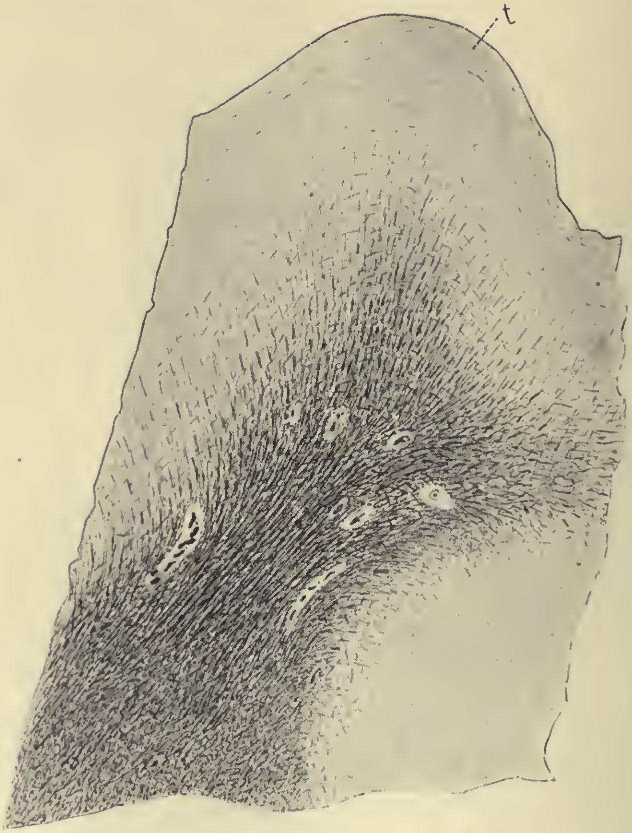

FIG. 11.—Section of the cortex at the point of origin of the left F^3 from the lower extremity of gyrus præcentralis (stained with Pal's hæmatoxylin). The tangential fibres, and those forming the infra- and supraradial plexus, are much rarefied; the same is seen in the medullary axis, and especially in the basal portion of the latter.

SUMMARY.

In the period between 1907 and 1909, the patient showed disturbances in his speech, which gradually increased, and consisted in the use of unusual words in ordinary conversation (paraphasia and echolalia). He also experienced difficulty in understanding many questions. After two years (March to August, 1909), the examination of the patient revealed true partial sensory aphasia (with automatic echolalia and perseveration), associated with paralexia and almost complete agraphia.

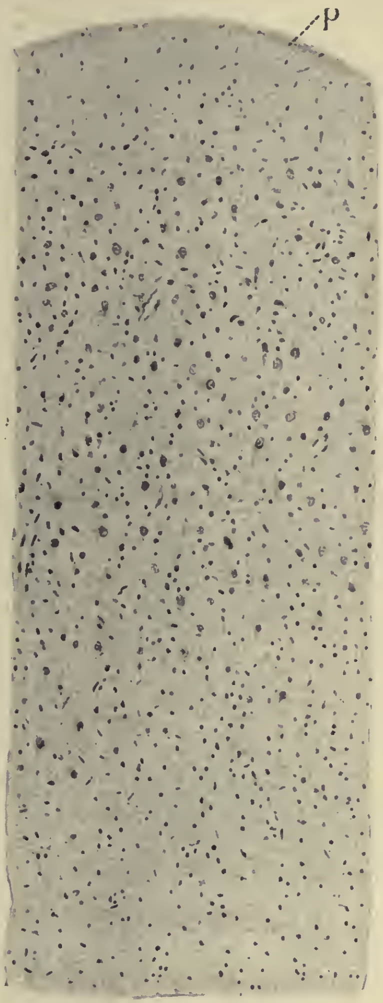

FIG. 12.—Section of cortex at the point of the passage from the pars opercularis of the left F^3 to the adjacent portion of the gyrus præcentralis. (Enlargement and staining the same as in figs. 7 and 10). The disappearance of the nerve-cells is much more noticeable than in the two sections 7 and 10, the pyramidal nerve-cells preserved being very few.

In February, 1910, the sensory aphasia had become almost complete and some dysarthria was noticed in his repetition of words. The understanding of words was extremely limited; further, a condition of advanced dementia showed itself, accompanied by symptoms of agnosia.

In October, 1910, the speech disturbances had become still more serious; the word deafness, the alexia and the agraphia were complete, while voluntary speech was almost entirely absent. Parallel with these progressive disturbances of speech a condition of mental weakness gradually developed, which at last became a true dementia and was attended with symptoms of agnostic apraxia, and psychical blindness.

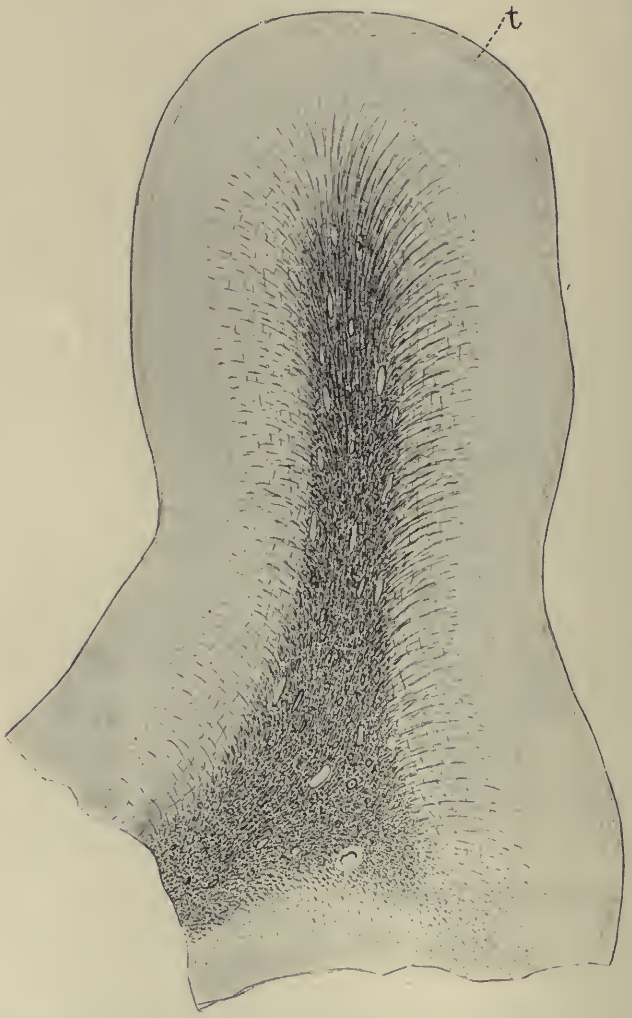

FIG. 13.—Section of the cortex of the pars opercularis of the right F³ (stained with Pal's hæmatoxylin). The medullary fibres are well preserved, except for a slight rarefaction of the fibres of the supra- and infraradial plexus, and on one side only of the section.

Two months later (four years after the beginning of the disease) the patient died.

The *post-mortem* revealed severe atrophy of the prefrontal and temporal convolutions, the left side being the most affected, while the histological examination showed severe alterations in the nerve-cells and medullary fibres of the convolutions belonging to the Broca region (*in sensu lato*) and to T^1, these changes being greatest on the left side.

Critical Considerations.

Having thus described this new case, it will be well to compare its clinical and anatomical features with the results obtained by other writers. The complex of symptoms is almost uniform, and consists of a double set of phenomena, of which one belongs to speech and the other to the mental processes.

In the case described by Bischoff, the power of understanding words was extraordinarily impaired, but that of the repetition of words was quite intact. At the autopsy, atrophy of both the temporal lobes was revealed, the left one being the most affected.

Liepmann's patient was able to speak spontaneously, though intercalating clear signs of paraphasia. He understood questions, but he first repeated them in an interrogatory form, and then replied. As the disease progressed, the patient no longer understood the sense of the words, which he still repeated, though without giving any reply (automatic echolalia) and his command of spontaneous words became much reduced. Macroscopic investigation revealed atrophy of the frontal and temporal convolutions, and especially of the apex of the left temporal lobe; the smallest of all were the left T^1 and T^2. Upon the pia were vesicles containing a clear liquid.

In their first case of aphasia, P. Marie and Léri did not record any appreciable alterations in the horizontal sections of the right hemisphere, the lateral ventricle was found to be dilated, and especially the upper portion of the occipital pole. In the subependymal region it seemed to be surrounded by a sclerotic zone, and the white matter of the hemisphere appeared much atrophied. In the cortex of the brain there were no lesions whatever.

In the second case of the same writers, where the patient was affected with typical sensory aphasia, abnormal dilatation of the left occipital cornu was also found.

In a case of Ascher's, which was not typical, inasmuch as motor aphasia, first temporary and afterwards permanent, was associated with paralytic dementia, there were found the usual lesions of this psychosis, further in the left T^1, the degeneration of the nerve-cells and of the white matter had reached a more advanced stage than in the rest of the brain.

In Shaw's case, the aphasic symptoms, consisting of word-blindness and word-deafness, suddenly manifested themselves; the patient was suddenly seized with paralysis of the right arm. The affection afterwards disappeared, but thenceforward the patient was afflicted with a slight incoherence of speech, and in addition showed signs of word-blindness and word-deafness. At the autopsy, atrophy was revealed of both the gyri angulares and of both the T^1 and T^2. This case is, however, exceptional, and it is very doubtful whether these disturbances of the speech were present before the occurrence of the stroke.

In Mills's case, where we have to do with a man who had suffered from complete word-deafness for thirty years, without any improvement in his condition, it was found at the *post-mortem* that there was considerable atrophy of T^1 and T^2 on both sides, but chiefly on the left.

In Edlich's patient, a change was first noticed in her character and manners, together with a reduction in her command of words; afterwards real motor aphasia gradually developed, associated with sensory aphasia, which was incomplete at first, but afterwards became complete, and was accompanied by agraphia and total alexia. The patient only showed signs of sensory apraxia. In the last stage of the disease, the patient's conduct was increasingly insane; she no longer recognized persons and rooms, wandered about aimlessly, rose at night, and displayed a marked tendency to laughter and tears. At the autopsy, the weight of the brain was found to be reduced to 893 grm. This decrease in weight was due to advanced atrophy of both the frontal lobes, while in the corresponding sulci the pia formed cysts as large as a hazel-nut. The parts most atrophied were the posterior portion of F^3 and the left insula.

In my case, No. 1 (published in 1902), which was that of a woman (illiterate), aged 67, the first symptoms appeared after a slight stroke; they consisted in in slight dysarthric troubles (the patient pronounced words badly and scanned them), in a reduction in her command of words, and in a slowly progressive incapacity for understanding the meaning of words. These symptoms continued to increase slowly; thus, a few months before her death, the patient did not understand a single word, and could only pronounce certain syllables (be, be, po, po, pa).

During this period, she performed foolish acts due probably to agnostic apraxia. She put her dress over her jacket, exchanged her spoon for her fork or knife, burst into laughter or tears without any reason. Examination revealed increased resistance in the limbs to passive movements. Reflex iridoparesis to the light, mostly on the left. Macroscopic and microscopic examination showed that the convolutions were reduced in volume, and that their external surfaces were shrivelled and dark in colour, especially on the left. The cerebral hemispheres were full of liquid. The grey matter of the cerebral cortex and of the cerebral ganglia were of a darker colour than usual. The weight of the encephalon was 1,000 grm. Histological examination (Nissl's technique and method) revealed a considerable amount of alteration in the nerve-cells of all the strata of the cortex, and especially in those of pyramidal shape. In the pars opercularis of the left F^3, a fair number of the nerve-cells were affected by a diffusion of pigment; in many, a good deal of the cytoplasm had disappeared, while some cells showed the characteristics of chronic alteration. In the lip of the calcarine sulcus and in the left T^1 alterations in the nerve-cells were relatively rare.

In the patient studied by Alzheimer there gradually developed, first motor aphasia, then partial sensory aphasia and lastly word-deafness. At the *post-mortem*, T^1 and the lobulus parietalis inferior were found to be darker than is normally the case. Microscopic examination revealed in these, degenerated convolutions, sclerosis and calcification of the nerve-cells, containing both large and small nuclei poor in chromatin. The medullary fibres of the corresponding cortex had disappeared. At the same time, in some of the brown spots of the above-mentioned convolutions, a large number of enormous pyramidal cells had made their appearance.

Veraguth's patient manifested, for a short time, symptoms referable to the subcortical form of sensory aphasia. Words sounded to him like a murmur, while his spontaneous speech was fluent and free from mistakes. At the *post-mortem*, there was discovered to be a considerable degree of atrophy of the posterior portion of the pars opercularis of the left F^3, and also of the median portion of the left T^1; these zones were reabsorbed and their places taken by a serous liquid. No microscopic alterations were met with in the injured part.

In Franceschi's patient a relatively short period of depression was succeeded by sufficiently clear symptoms of sensory aphasia, together with signs of extreme dementia. The latter revealed itself both in serious lapses in behaviour, and in the fact that the woman was unable to answer questions coherently. Neurological investigation disclosed cutaneous hyperalgia, loss of the plantar reflexes and exaggeration of the patellar and Achillis reflexes (without clonus). There was noticeable atrophy of the three left temporal convolutions. In the cerebral cortex corresponding, many nerve-cells had either disappeared, or undergone alteration, this being especially the case with the pyramidal cells. In the zones whence the nerve-cells had disappeared, there were many glia elements, both in the grey and the white matter. A slight rarefaction of the radial and of the transverse nerve-fibres was also recorded, together with an absence of the tangential fibres. These alterations were much less evident in the right temporal convolutions.

Pick studied three cases of the kind. The first was a woman, aged 58. The disease had begun two or three years before with symptoms of dementia in the form of loss of memory and serious loss of the power of identification; she believed that her son was one of her nephews, that the house she inhabited was her own property, &c. Upon this, followed an actual loss of all capacity of orientation; the patient no longer knew the time, and could not find her way to church. An examination, made at this time, revealed difficulty in finding words and in understanding their meaning. Thus, the patient was incapable of understanding the sense of words, but she repeated them correctly and in the form of a question. Two years later, the dementia had made rapid progress, and the patient no longer comprehended any questions, while her command of words was reduced to the use of a few stereotyped phrases.

Pick's second case was that of a woman, aged 75, who had already been ill for three years when she came under his observation. She began to show signs of want of power of orientation, pulled up the vegetables in the garden and went out of her house for no purpose. Her comprehension of questions was most limited, so that she gave one the impression that she had become almost deaf. She could write well if she copied (servile writing). Some months later, the disturbance of her speech became more serious; a jargon-aphasia prevailed, both in her spontaneous speech and when she named objects. Her command of words had continued to become more limited, with a tendency to the repetition of the same phrases.

The third case was that of a woman aged 38, suffering from progressive paralysis, in which numerous oculo-motor disturbances were accompanied by hypokinesis of the lower branch of the seventh right nerve and noticeable dysarthria and exaggeration in the patellar reflexes.

The investigation of her speech revealed the presence of paraphasia (of the verbal and syllabic type), less evident during emotion. But the dominant symptom was amnesia verborum; the patient when asked to name an object always replied "I do not know what it is."

At the *post-mortem* of the first case was found a considerable atrophy of the convolutions, and especially of the left frontal and temporal gyri. In the second case, the atrophy of the encephalon was so great that its weight was reduced to 967 grm. The affection extended to all the convolutions, but was most marked in the left temporal lobe. The condition of the third case was almost identical.

In my present case (No. 2), the patient began first to show signs of partial word-deafness, which were very soon followed by symptoms of agnostic apraxia, amnesia verborum, paralexic troubles, and almost complete agraphia. Later, the sensory aphasia became complete, and was associated with dysarthria in repetition; while the patient's command of words became increasingly limited, and the dementia increased. At last, the agnostic disturbances became extreme, the pre-existing symptoms of aphasia became aggravated and more evident, while the patient's spontaneous speech became reduced to the repetition of the stereotyped words "Don Antonio," and complete loss of comprehension of words and total agraphia followed.

The *post-mortem* revealed a considerable amount of atrophy of the prefrontal lobes, especially of the pars opercularis of the F^3, and of the upper temporal convolutions, the left being more markedly affected than the right, and particularly in the middle portion. Microscopic examination of the cortex of the more affected convolutions showed the presence of a true process of degeneration affecting the nerve-fibres of the medullary axes, the superior and inferior plexuses and the tangential fibres; the nerve-cells of the cell strata of the cortex were severely altered; the nerve-cells of the motor word area had suffered more than those of the auditory word area; and those on the left side were more affected than those on the right.

The symptoms of the Dejerine and Sérieux case coincided (Liepmann) with the complex of transcortical sensory aphasia, all the more since difficulty in reading and writing were uncommon. The Dejerine-Sérieux patient, in fact, was affected by a slighter degree of echolalia, namely, in the form of asking questions, and did not get as far as subcortical sensory aphasia (Pick). Further, the essential feature of this last type of aphasia is that speech is not apprehended as such, and therefore is neither understood nor repeated, while the other speech functions are intact. In Dejerine's case, on the other hand, the patient repeated the questions, although, as a rule, he did not understand the sense. In writing from dictation, he was faithful to the sounds of the words, and the chief mistakes were those which anyone (writing) would make, through failing to understand the sense of what was dictated. At the *post-mortem* was found symmetrical atrophy of the temporal lobes, which above and before were reduced to half their normal volume, so that the insula was exposed. Their cortex had more consistency than that of the rest of the hemispheres; the pia was adherent, microscopic examination revealed the disappearance of the tangential fibres of the nerve-cells of the molecular strata, of the fibres of the radii and the short association fibres, as well as a decrease in the number of the pyramidal cells, especially in that of the small ones.

Rosenfeld's first patient (a man, aged 62) was sufficiently correct in behaviour during the early stage of the disease, but he was less active and played chess all day. His powers of reading, writing spontaneously, of copying, and of understanding and speaking spontaneously were perfect. With the passage of time (eight years) his power of criticism weakened, as did also his capacity for association of ideas. The neurological examination carried out one year before his death (i.e., when he was received into the hospital) showed that the motion and reflexes, &c., were normal; verbal amnesia was very noticeable; he was able to read and to write from dictation. On the occasion of a second examination it was observed that the conditions of speech were unchanged, though he uttered few words spontaneously. The speech disturbances remained the same until the patient's death, which took place one year later. At the *post-mortem* the left temporal lobe was found to be much reduced, the atrophy having chiefly affected T^2 and T^3. T^1 was relatively larger than either of the latter. The convolutions (including the apex) of the right temporal lobe were smaller than normal. Microscopic investigation showed that in the medullary zones, which were much reduced, the perivascular lymphatic spaces were notably dilated, and that an enormous number of nerve-fibres had disappeared from the cerebral cortex. The number of the ganglion cells were greatly diminished, but they had mostly preserved their fibrillary structure; the nucleus was, in general, well preserved; it was surrounded by a granular substance.

In Stransky's case it was noted that the patient could not understand the sense of many words, and showed a tendency to reply, repeating first the question addressed to him (not automatic echolalia), but evinced little inclination to speak spontaneously. He could repeat correctly what he heard, and also some songs, but nothing else at will; he also showed, in general, a tendency to word-perseveration. He used to read aloud, but with evident paralexia, and he did not clearly understand what he read. He was incapable of writing, and even of copying. Flexibilitas cerea was evident. The patient was unable to recognize the use and significance of the commonest objects. He manifested a tendency to echopraxia, servile imitation of what he saw others doing. At the *post-mortem* atrophy was found to be present, especially on the left side, some special parts of the cerebral convolutions being affected, i.e., the middle part of gyrus calloso-marginalis, the cuneus, the præcuneus, and, above all, gyrus supra-marginalis; the atrophy of the said zones on the right was much less noticeable.

As a general conclusion we find that aphasic disturbances are not always uniform. In some cases the prevalent symptom is perceptible even to lay minds, as it consists in an incapacity to comprehend the meaning of words and of a considerable number of questions, and it manifests itself early. Gradually, the disturbance becomes more and more noticeable, and finally the patient becomes indifferent to all questions. In the development of aphasic troubles, occasionally the intervention of true paraphasic troubles, of the verbal and syllabic type, has been recorded, sometimes amounting to jargon-aphasia, or perseveration. Dysarthric disturbances are of rare occurrence (in Pick's first case and in my patients No. 1 and No. 2).

Sometimes the patients, though understanding the questions, repeated them before replying (simple echolalia); with the progress of the disease, this echolalia always assumes the automatic form, for the patients repeat the questions, almost as if obliged, though they do not understand their signification. With sensory aphasic disturbances are often associated, from the commencement, difficulties in recalling and pronouncing words. Occasionally these symptoms precede the sensory aphasia. The first signs are an incapacity for finding words—amnesia verborum—which later on gives place to a progressive reduction in the command of words, and also to an incapacity for repeating pronounced words. This trouble always increases with time, so that finally every effort of the patient to speak merely results in the utterance of one or two words, or of some syllables (in my first case the patient said be, be, po, po, pa, pa) or at most a few stereotyped phrases (Pick's cases 1 and 2, my case No. 2). In a few cases it is almost impossible to judge whether the progressive aphasia proceeded parallel with the loss of the memory of the words, or if it was only consequent on an inability to recall the motor images of an always greater number of words.

Many of the patients examined were illiterates, which accounts for the lack, in the greater number of cases, of notes respecting their capacity for reading and writing. In rare cases, the power of reading and writing remained unimpaired throughout the course of the disease. As a rule, the patients at first understood what they read, but made mistakes when reading aloud (paralexia), but they always finished by being unable to pronounce the words they read, much less could they understand them (word-blindness). Sometimes the capacity for writing was partially retained; the patients could write to dictation and could copy. Sometimes difficulties in writing (servile writing) showed themselves, either at the beginning or during the progress of the disease, and generally increased almost parallel with the development of the sensory aphasic troubles, so that in the end the patient was unable to write at all.

Parallel to the aphasic disturbances, disorders of the other mental processes developed. At the beginning of the disease the patients neglected their business, became less efficient, and showed less capacity for work, and above all, their critical faculty became weakened. With the progress of time they forgot things to an enormous extent, seemed to have no idea of time or of place; they were unable to distinguish persons, and no longer recognized the faces of their friends or the aspect of rooms, but wandered about aimlessly, arose during the night, pulled up plants in the garden, and no longer knew how to dress themselves, sometimes putting on only one shoe or one sock. Sometimes they showed actual signs of dyspraxia, usually of the agnostic type, putting a dress over a jacket, using a spoon instead of a fork, putting socks over their hands, perhaps in consequence of partial psychical blindness. This symptom-complex is always completed by exaggerated emotion which culminates in spasmodic laughter or tears (Edlich's case) usually without adequate cause (my case No. 1.)

Paralytic symptoms rarely manifested themselves during the course of the disease. In my case, No. 2, there was slight facio-lingual-brachial hypokinesis with an exaggeration of the tendon reflexes of both sides and sometimes with clonus of one foot. In Shaw's case partial paralysis of the right arm is recorded; this, however, afterwards disappeared. In Liepmann's patient there was, in addition to a slowness in pupillary reaction, a tremor of the hands and tongue. The patient walked insecurely, and with his legs far apart.

The age at which the disease declares itself varies from 38 to 67; it attacks men and women about equally. Its course is rather slow and progressive, the exact date of its beginning is difficult to determine. In general the disease lasts from two to eight years, with an average duration of four years. Mills alone states that in the case of his patient the malady had lasted for thirty years.

As for the macroscopic and microscopic data recorded by the various writers in studying their cases, it can be stated that the fundamental change consists in an atrophy of the cerebral convolutions, and that the atrophy is not uniform, either as regards the different lobes affected or as regards the right and left halves of the brain. The alterations are generally more pronounced on the left side. In some cases there occurred a dilatation of the lateral ventricle, especially of the occipital cornu (Marie's second case). Occasionally this dilatation is associated with atrophy of the medullary matter of the hemispheres, and with sclerosis of the subependymal region (first case of P. Marie and Léri). At other times it is a question of an atrophy of all the cerebral cortex (my case No. 1), but chiefly of the left T^1 (Ascher's case, Pick's second case), or else the atrophy is limited to one part of the parietal and temporal lobes, i.e., to the gyri angulares and to T^1 and T^2 (Shaw), to both T^1 and T^2 (Mills), to the supramarginal gyrus, to the cuneus and to the præcuneus (Stransky), to the upper and anterior portions of the temporal lobes (Dejerine and Sérieux), or to the three temporal convolutions, especially the left (Franceschi). Sometimes the atrophy affects the frontal convolutions as well as the temporal (my case No. 2 and Pick's cases 1 and 3), or the frontal convolutions of both sides, and the left insula (Edlich).

The histological examination of the cortex of the atrophied convolutions, which has hitherto seldom been made, reveals varicose swellings of the fibres and almost always the disappearance of many of the transverse fibres of the infra- and supraradial plexuses. Almost without exception a greater or lesser number of the nerve-cells have disappeared in an almost regular manner from all the strata. Nearly all the nerve-cells which have been preserved show signs of pronounced modification, which consists in the pigmentation and reabsorption of the cytoplasm. Occasionally an increase was observed in the cells of the glia of part of the atrophied convolutions. A parallelism does not always exist between the alterations of the medullary fibres and those occurring in the nerve-cells (my case No. 2).

In Alzheimer's case the nerve-cells had undergone degeneration and were sclerotic and calcified; the nuclei were poor in chromatin and there were giant pyramidal cells at the same level in some of the convolutions, which were of a darker colour than normal. It may be said, briefly, that the lesion causing the aphasic symptoms consisted of an atrophy, which rarely extended to the whole cerebral cortex, but was limited, although not exclusively, to the temporal convolution, or else to the frontal lobes, usually the left one. The corresponding histological alteration resolves itself principally into a primitive degeneration of the nerve-cells and medullated fibres of the grey matter of the cortex, and of the axis of the convolutions.

The reasons that atrophy at one time attacks all the cerebral cortex, and at another only affects certain parts, are at present quite unknown to us. It is impossible to conceive that this difference of behaviour can depend upon the method of the distribution of the arteries, for this hypothesis would not explain why the disease sometimes spares the gyrus præcentralis, or why the middle of the gyrus temporalis supremus is much more frequently attacked than the extremity. Sometimes an evident parallelism can be observed between some of the aphasic disturbances and the seat of the macroscopic cortical changes. In those cases where the sensory-aphasic symptoms are dominant (Mills, Bischoff, Dejerine, Liepmann, Franceschi, Pick's case No. 2), the only atrophied convolutions were exclusively, or generally, the gyri temporales 1 and 2. On the other hand, motor-aphasic symptoms were associated with sensory-aphasic disturbances (my cases 1 and 2, Pick's case 1, Edlich), atrophy also attacked the pars opercularis of F^3, together with the other convolutions of the prefrontal lobe. Nor should it be forgotten that in Shaw's case, and in my case 2, in which symptoms of word-blindness were also recorded, the left gyrus angularis was noticeably more atrophied than the other convolutions.

The relation between the cortical zone, which is the seat of the atrophy, and certain special aphasic symptoms ought, however, to be further investigated. It may here be called to mind that, according to some investigators, the fact that amnesic aphasia gradually produces loss of command of words is due to the ever-increasing affection of the temporal convolutions, while others hold that under these circumstances the process is not limited to the temporal lobe, but extends to the other zones of the hemispheres. This is the opinion of Pick; he points out that in the course of senile atrophy of the brain, even where the temporal lobes are also much atrophied, no noticeable loss in the command of words occurs, even if the patient no longer understands what he is saying. According to Pick, the decrease in the command of words is a sign that F^3 is attacked. This idea is confirmed by my case where not only T^1 was affected, but the whole of the pars opercularis of F^3.

As for the word-deafness, Pick holds that, in his case, it was not a question of want of perception of words, because the atrophy had not begun in T^1. Rosenfeld is of the same opinion, since his patient, though he was ill for about eleven years, never lost his power of understanding words (nor did his command of language decrease). Macroscopic investigation showed that the T^1 was relatively little affected, and that the atrophy had chiefly attacked T^1 and T^2, together with the gyrus occipito-temporalis. This opinion is also confirmed by my present case, since the right T^1 and T^2, especially in the median zone, were much atrophied, together with those on the left side, and the histological alterations of the corresponding cortex were considerable, particularly on the left side, while my patient had almost completely lost the power of understanding the significance of words. This, on the other hand, tends further to confirm the belief of the bilateral nature of the seat of auditory word images.

Opinions are at variance concerning the seat of amnesia verborum. Rosenfeld is inclined to think that the centre for the recollection of names is to be found, on the left, in these three convolutions (T^2, T^3, gyrus occipito-temporalis), because these were the most affected in his patient. Quensel, on the contrary, holds that a morbid process going on in the gyrus angularis and in part of the gyrus supramarginalis (the so-called "via sensoriale anacentrale") should produce symptoms of amnesic aphasia. This opinion is not shared by Rosenfeld, who could not record any considerable reduction in these cerebral regions of the brain of his patient. Others, in conclusion (Wolff, Dejerine), hold that it is impossible to localize amnesic aphasia, since it forms a part of motor aphasia, and depends upon a diffused morbid process affecting the cerebral cortex. Rosenfeld, however, draws attention to the fact that this opinion cannot be unconditionally accepted, for in his patient's case there was certainly a diffused morbid process, but this extended chiefly to the said three convolutions (T^2, T^3, gyrus occipito-temporalis). From the data of my present case, it is impossible to come to a conclusion in favour of either view, for while it is true that the three convolutions just mentioned were atrophied, if only partially, nevertheless the left gyrus supramarginalis and angularis, as well as the convolutions of the prefrontal lobe, were also affected to a considerable degree. We could, therefore, only logically deduce from this, that amnesia verborum is not due to a process diffused throughout the whole cerebral cortex. However, it would be illogical, since sufficient proof is lacking, to state that the rest of the cerebral cortex was sound, only because the volume of all the other convolutions was apparently normal. It will therefore be wise provisionally to look upon the most various zones, of the cerebral hemispheres, at least to some extent, as the anatomical ground of amnesic aphasia (v. Monakow and others).

Amongst the disphasic disturbances which sometimes occur during the course of aphasia due to atrophy of the convolutions, echolalia is mentioned. The seat of this symptom is also very far from determined. There are two kinds of echolalia: the one consists in the repetition, in the form of a question, of that which has been asked, and which has been understood (Pick), and the other in an automatic, forced repetition (echolalia automatica). Now, since the path of speech, by means of which the repetition is effected, is the oldest in ontogeny (as is shown by the development of speech in young children), it is clear why the second kind of echolalia occurs in the case of senile atrophy which is confined to the left temporal lobe, only at a stage when the sense of words is no longer understood (Liepmann) and, in truth, if the stimulation of the sensory centre of speech no longer awakens any response in the other cortical regions, it finds a vent along the more ancient path of speech (motorial path).

It therefore follows that it is impossible for the complete physiological separation of the temporal lobe from the other speech zones to arise from the atrophy of the temporal lobe alone, and it is thus logical to think that other parts of the cerebral cortex are also involved, and, therefore, that forced automatic echolalia represents a very marked degree of sensory transcortical aphasia, and hence is only found in serious degradation of the psychic functions. Accordingly it is not to be wondered at if two of Pick's cases (Ruczica and Pal) in which automatic echolalia occurred, manifested in the highest degree general atrophy of the brain and of the left cerebral hemisphere in particular. In the case of my patient No. 2 also, where atrophy had not only extended to the temporal lobe but also to the frontal lobe, the echolalia had become automatic only three years after the beginning of the illness. In Dejerine's case, on the other hand, where the brain was normal, with the exception of the two temporal lobes, the symptom in question was entirely absent. The same may be said of Liepmann's case, in which there was atrophy of the left temporal lobe alone. Perhaps the simultaneous atrophy of the right temporal lobe may contribute to automatic echolalia; that hypothesis is favoured by the case of my patient, where the cortex of the right gyrus temporalis supremus also presented histological alterations.

It is thought that the study of cases of partial atrophy of the brain may open the way for the acceptance of the belief in the localization of psychic functions, and therefore that these cases might form the point of departure for a topographical psychology. Unfortunately, the problem is far less simple. Here, it is true, we have a limited loss of large nerve elements which present a functional, and perhaps an anatomical unity. Nevertheless, in these cases, it is not permissible to establish a connexion between clinical symptoms and histological data, both because the intelligence of the patients who present themselves for examination is already so much enfeebled that it is impossible to investigate exactly the psychic symptoms, and because also they are sometimes suffering from word-deafness. Thus in the case of my patient it was impossible to undertake my researches in this direction, and we were obliged to content ourselves with the study of his behaviour and conduct.

The data reported in the preceding pages testify clearly to the importance of the frontal lobes for eupraxia. Thus, Pick noted that one of his patients, who was suffering from serious atrophy of the frontal lobe, experienced difficulty in managing objects in common use. He, however, believes that this motor apraxia (in truth somewhat mixed) depended upon the atrophy being limited to the frontal lobe. In my cases Nos. 1 and 2, in which the atrophy of the gyri præfontales was also very great, the apraxic symptoms had attributes which were entirely those of extreme visual agnosia. At any rate it is not necessary to conclude that the aphasic and asymbolic (apraxic) manifestations are due to dementia, since sometimes, as in Edlich's case, dementia may not have already declared itself clearly at the period when the said symptoms prevailed.

I will remind the reader in this connexion of the phenomena of psychic blindness present in my case No. 2, and also in others. Psychic blindness and amnesic aphasia often proceed *pari passu.* To understand this, it is only necessary to remember that speech is a highly differentiated mental process, which has been acquired late in ontogeny, and is readily affected by any decrease in psychic power. This is shown by the difficulty in speaking experienced on waking, and when suffering from fatigue, or from any shock, although other functions remain intact.

In old age, the difficulty found in recalling words is due to an incapacity of raising the optic stimulus to the point of producing a response in parts which, in their turn, have become difficult to excite. Therefore, in the greater number of cases of pure cortical blindness, we find a certain amount of amnesic aphasia present; this shows that the stimuli conveyed to the visual cortex, and the revival of the conceptual complexes, are no longer sufficiently strong, if the zone of the sensory aphasia begins to atrophy, and that, further, mental visual stimuli will not succeed in evoking them. If, then, both the spheres are affected by incipient atrophy, but one more seriously than the other, as in many of our cases, it is clear why, even from the beginning of the disease, amnesic aphasia is a symptom often associated with visual agnosia. For this reason disturbances, similar to those which accompany psychic blindness, are often found in our cases. Let me remind the reader of the difficulty in recognizing objects, in recalling immediate images and names, the increased slowness of identification, the feeling of disorientation, the want of visual attention, and hence the difficulty of comprehending the whole together with the parts. All these troubles we find present, and a little accentuated, in the beginning of old age (Stauffenberg); and in fact to-day the pathology of the cerebral cortex has taught us that cortical plaques (a cytopathological sign of senility) are to be met with as much in incipient normal old age, as in eyes of old persons affected by conspicuous mental weakness (F. Constantini).

The results of the microscopic investigations of the circumvolutions when compared with the different clinical pictures reported in the foregoing pages, confirm us still more in the belief that the different forms of aphasia dependent upon the atrophy of the gyri are specially due to the degeneration or the disappearance of the nerve elements lying in defined cerebral regions. In fact, the researches have taught us that echolalia only becomes automatic when the atrophy extends beyond the left temporal lobe, whereas if it is confined to this lobe the disturbance consists only of a partial sensory aphasia. Further, symptoms of motor aphasia (reaching the point of dumbness) are associated with the preceding troubles only when F^3 and the insula participate in the atrophy, and finally, the wider the atrophy becomes diffused the more clearly do the sensory aphasic disturbances and the signs of dementia manifest themselves. This does not testify completely in favour of the idea that the whole cerebral cortex contributes to the comprehension of the signification of heard verbal symbols (v. Monakow). Certainly, the more difficult it is to evoke a representative image in consequence of the extension of the atrophy over the various regions of the cortex, the more marked will be the difficulty in recalling words, and if the processes of mental synthesis become difficult owing to the same pathological cause, the comprehension of what is read, or heard, also is attended with greater trouble.

It would be very daring to deduce from such a small number of cases, some of which have been reported in a summary manner, criteria for determining during life whether a certain aphasic syndrome is due to progressive atrophy of the cerebral convolutions, or whether it depends upon a destructive focus situated in the speech region. But, in any case, a few considerations may be of some use in enabling us to proceed to a differential diagnosis. Points in favour of a cortical, or subcortical, focus of destruction are the sudden manifestation of the aphasia, or at any rate the existence of transitory prodromal symptoms only. On the other hand, in cases of aphasia due to atrophy of the convolutions, a stroke is nearly always absent, the speech troubles begin and increase with excessive slowness, so that it is difficult, even approximately, to determine the time of the appearance of the first symptoms. Nevertheless, sometimes, as in the case of Shaw's patient and of my No. 2, the first speech troubles were recorded as occurring immediately after a species of stroke, which was followed by transitory paresis of the limbs. A second criterion for differentiating between the various kinds of aphasia is the simultaneous presence of severe paralysis of the limbs, since facio-linguo-brachial monopareses (or monoplegias) are often associated with aphasia due to the destruction of the speech zone, especially in motor aphasia, or hemiparesis of the right side, which is sometimes flaccid and sometimes spastic, according to the extension, the seat, or the date of the beginning of the lesion. Motor troubles of such severity are never observed in cases due to atrophy of the convolutions. However, the presence of slight paresis of one side is not irreconcilable with the disease in question; it is only sufficient to call to mind my No. 2, in which the muscular strength of the right side was weaker than that of the left, and in which there also was present paresis of the right half of the tongue. Frequently also, in aphasia following the atrophy of convolutions, the action of the tendon reflexes is on both sides; this does not occur in aphasia due to the focal lesions. It may, however, happen that the Achilles reflexes are exaggerated on one side, even to the point of foot clonus (my case No. 2).

Hence, it follows that in some cases, and especially when a clinical history is absent, which could furnish us with precise data as to the manner in which the aphasic troubles have developed, it will not be easy to give an opinion on the pathogenesis of the aphasic symptoms. In the present case, indeed, I succeeded in forming a correct judgment during life, basing my conclusions upon the fact that the sensory amnesic and aphasic troubles had developed slowly, that notable disturbances in the motor power, of the limbs at least, were wholly absent, and finally, that the patellar and the superior tendon reflexes were equal on both sides.

Sometimes it may be doubtful, especially where symptoms of word-deafness are dominant, whether the incapacity to understand the meaning of any question whatever is a sign of simple senile dementia. Nevertheless, analysis of the symptoms will always form some basis from which to arrive at a correct decision. Thus, for example, even in the most advanced stages of this psychosis, the patients always understand a certain number of questions, and do not reply like an echo, much less do they lose all command of language to such an extent as scarcely to be able to use one or two words. On the other hand, even in the total wreck of the intellect, such as occurs in advanced senile dementia, loss of the memory of graphic symbols has never been observed.

BIBLIOGRAPHY.

[1] Alzheimer. "Ueber perivas. gliose.," *Allg. Zeitschr. f. Psychiat.*, 1897, Bd. liii, S. 863.

[2] Beitrach. "A Case of Traumatic Aphasia," *Arch. of Med.*, 1885, vol. xii, p. 233.

[3] Bischoff. "Beitr. z. Lehre d. sensor. Aphasie," *Arch. f. Psychiat.*, 1899, Bd. xxxii, S. 730.

[4] Clark, P. "An Anomalous Case of Aphasia," *Journ. of Nerv. and Ment. Dis.*, 1894, vol. xxi, p. 703.

[5] Dejerine and Sérieux. "Un cas de surd. verb. pure," *Comptes. rendus. de la Soc. de Biol.*, 1897, t. xlix, 10me sér., iv, p. 1074.

[6] Edlich. "Ein Beitrag. z. Kenntniss d. Aphasie," Greisswald, 1902, Inaug. Diss.

[7] Franceschi. "Gliosi perivascolare in un caso di demenza afasica," *Annali di Neurol.*, 1908, vol. xxvi, pp. 281-290.

[8] Liepmann. "Ein Fall v. Echolalie," *Neurol. Centralbl.*, 1900, Bd. xix, S. 389.

[9] Marie et Léri. Soc. Neurol. de Paris, Séance du 2 juin, 1904, in *Rev. Neurol.*, 1904, t. xii, p. 636.

[10] Mingazzini. "Klin. u. anatom-pathol. Beitr. über Aphasien," *Deutsch. Zeitschr. f. Nervenheilk.*, 1902, Bd. xxi, S. 386.

[11] Pick, A. "Zur Symptomatol. d. linken Schläfenlappenatrophie," *Monatschr. f. Psychiat. u. Neurol.*, 1904, Bd. xvi, S. 378.

[12] Rosenfeld. "Die part. Atrophie der Gehirnwindung," *Journ. f. Psych.*, xiv, H. 3 u. 4.

[13] Shaw. *Brit. Med. Journ.*, 1892, vol. i, p. 438, cit. in Mills, *Brain*, 1891, vol. xiv, p. 467.

[14] Sorel. "Aphasie, epileps. jackson.," *Rev. de Méd.*, 1881, t. i, p. 1011; *Neurol. Centralbl.*, 1882, Bd. i, S. 39 (Abstract).

[15] Stransky. "Zur Lehre von den aphasischen," &c., *Monatschr. f. Psychiat. u. Neurol.*, 1903, Bd. xiii, Erganzshft., S. 499.

[16] Veraguth. "Ueber einen Fall von trans. reiner Worttaubheit," *Deutsch. Zeitschr. f. Nervenheilk.*, 1900, Bd. xvii, S. 177.

[17] Westphal. "Klinischer u. anatomischer Beitrag zur Aphasie-Lehre," *Allg. Zeitschr. f. Psychiat.*, 1907, lxiv, S. 169.

A STUDY OF THE SATELLITE CELLS IN FIFTY SELECTED CASES OF MENTAL DISEASE.

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IN the normal cerebral cortex, both human and animal, there are found at the base of many of the large pyramidal cells one or two small cells lying between the basal processes and, as a rule, in close association with the point of origin of the axis-cylinder.

There has been some question as to whether these cells should be regarded as neuroglial in origin, or cells of the lymphocytic series. By the ordinary staining methods their morphology is very similar to that of the lymphocyte, except that the nucleus is often less deeply stained and bears a more loosely woven chromatin mesh, while some even appear vesicular. On the other hand it is rare, even among the vesicular forms, to find a nucleus which is oval, or as large as the ordinary glia cell. The lymphocyte is not as a rule an active phagocyte, while the satellite seems prone to take on neurophagocytic activity. In conditions associated with marked perivascular extravasation, such as general paralysis and chronic meningitis, the lymphocytes are closely packed in the perivascular spaces, but do not apparently tend to penetrate the surrounding nervous tissues. Many such cases show, it is true, a more or less active satellitosis, but this reaction is almost without exception in the deeper cell laminæ, while the perivascular accumulations are diffuse, or even more intense in the superficial layers.

Cajal accepts the neuroglial origin of these cells and speaks of them as basal neuroglia cells. He calls attention to the fact that they are in relation with that part of the cone of origin and early course of the neuraxon which is not covered with myelin, and suggests that they may serve to insulate these structures from surrounding non-medullated fibres. In the cerebellum of the rabbit, he has described a cell which he classes as a displaced stellate cell of Golgi. In the cerebellum of the majority of animals those cells are found in the granule layer and give off non-medullated axons which arborize in the granule layer. The displaced cells in the rabbit lie in the plexiform zone and their axons would thus be exposed to contact with other bare fibres of this layer. Cajal states that these cells may be recognized not only by their morphology but by the mass of accompanying nuclei of the neuroglia type which surround the axon and base of the cell, and here again suggests an insulating capacity for the satellite.

In pathological conditions the satellite becomes of greater interest. Especially is this true of the acute degenerative conditions which have been studied by Alzheimer in great detail by the aid of special staining methods. These include the toxic and infective deliriums and the experimental toxic states, as well as the severe acute manifestations of such diseases as katatonia, status epilepticus and the acute delirious type of general paralysis. In these conditions the cells at the bases of the pyramids are increased in number and show, with appropriate staining methods, a large protoplasmic body which may take on amœboid forms, may contain lipoid, or fuchsinophile, or other granules, and may be actively neurophagic. Alzheimer's work leaves little doubt that these reactive cells are of glial origin, but of a type not active in the production of fibres.

Another change in the normal relation of these cells is that of increase of number without the variety of alterations observable in the acute processes. This is the condition spoken of as satellitosis, and its occurrence has been noted in a number of diseases. As a rule the increase is most noticeable in the deeper cell laminæ of the cortex, and it is rather the exception to see any considerable number of them above the stellate layer.

The fifty cases forming the basis of the present study were selected to form five groups of ten each. These are: Maniacal depressive insanity, dementia præcox, senile dementia, general paralysis and alcoholic insanity. All three types are included among the dementia præcox cases, while the cases of the senile dementia group have been selected to exclude those showing gross brain disease, but not those showing moderate cerebral atrophy or arteriosclerosis.

With few exceptions the counts have been made from material fixed in alcohol, embedded in paraffin, cut at 10 μ and stained with Nissl's soapy methylene blue. The exceptions are from cases in which the brain was fixed in toto in formalin. This material was also cut into sections by the paraffin method at 10 μ and stained in thionin, so that the results should be comparable within reasonable limits of error. In all cases five areas from the neopallium were examined. The sites of the sections were as follows:—

Precentral or motor cortex (PCl.): Block taken from about the mid-portion of the ascending frontal or precentral gyrus in approximately the arm area.

Postcentral cortex (PoCl): Block taken from the ascending parietal or postcentral gyrus opposite the precentral block.

Frontal cortex (F.): Block from the first frontal gyrus along the margin of the great longitudinal fissure about midway between the frontal pole and the Rolandic fissure. In some of the cases this block yields sections showing a stellate layer and hence belongs in the true frontal type of cortex (Campbell's classification). Some showed no definite stellate layer (indicated in the tables by an absence of figure in lamina 4) and hence probably belong in the intermediate precentral field.

Temporal cortex (T.): Block from the first temporal gyrus, lateral surface along the lip of the fissure of Sylvius about midway between the line of projection of the anterior sylvian trunk and the point of division of the posterior or main sylvian fissure and hence representing auditopsychic cortex.

Occipital cortex (Occ.): This material is not constant in origin. Some sections are of calcarine or visuosensory cortex and some are of the common occipital or visuopsychic field. The sections from the calcarine area may be identified in the charts by the absence of a figure in the lamina ganglionaris, as no attempt was made to count the satellites in this layer as will be explained below.

The count has been made to include the two major points of interest, viz.: The number of satellites and their distribution by laminæ. Brodmann's division of the neopallial cortex into six layers—i.e., (1) zonalis, (2) granularis externa, (3) pyramidalis, (4) granularis interna, (5) ganglionaris, and (6) multiformis—has been adopted for this purpose, and an attempt has been made to count only cells which conform to the type of each layer. Thus in the lamina pyramidalis only large pyramidal cells have been counted, &c. This leads to some difficulty in some cortices, such as the precentral and agranular frontal which are without a well-developed lamina granularis interna and in the calcarine where the granule layer is reduplicated and the lamina pyramidalis is not well supplied with characteristic cells homologous to those in other regions. It has seemed advisable, however, for the present purpose to use one classification for all cortices, and hence the counts are made with the omission of a figure in lamina 4 of the precentral and agranular frontal, and in lamina 5 of the calcarine, while the reduplicated lamina granularis interna of the visual cortex has been considered as one layer. No effort was made to estimate the numbers of neuroglia nuclei in the zonal layer.

In each lamina the count has been made by recording the number of satellites found in association with 20 representative cells and record is made in increments of 10. Thus the association of 20 or less satellites with 20 nerve-cells has been considered negative; from 21 to 30 satellites with 20 nerve-cells is considered as a ratio of 1·5 to 1; 31 to 40 satellites, to 20 nerve-cells, as of 2 to 1, &c. Only those cells in immediate relation with a nerve-cell have been counted, and no cognizance is taken of the clusters of neuroglia nuclei about vessels, nor in spaces in the fibre layers which may have originally contained nerve-cells.

RECORD OF COUNTS.

I.—Maniacal Depressive Group.

Case 1.—Maniacal depressive insanity; maniacal form. Third attack; eleven years' duration.[1] Age at death, 65 years. Autopsy number, xv-15.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	1—1	1—1	1—1	0	0
(4)	—	1—1	1—1	0	1—1
(5)	1·5—1	1—1	1·5—1	1·5—1	—
(6)	1·5—1	1·5—1	2—1	2—1	1·5—1

Case 2.—Maniacal depressive insanity; depressed form. Third attack; duration twenty-seven years. Age at death, 68 years. Autopsy number, xvi-34.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	1—1	1—1	1—1	0	0
(4)	—	1—1	—	0	0
(5)	1—1	1·5—1	1—1	1—1	—
(6)	1·5—1	1·5—1	1·5—1	1·5—1	1—1

Case 3.—Maniacal depressive insanity; depressed form. Three years' duration. Age at death, 61 years. Autopsy number, xvi-42.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	1—1	1—1	1—1	1—1	0
(4)	—	1—1	1—1	1—1	1—1
(5)	1—1	1·5—1	1—1	1—1	1—1
(6)	1—1	2—1	2—1	1·5—1	1—1

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[1] In the maniacal depressive series the duration is given as from the time of onset of the first attack.

Case 4.—Maniacal depressive insanity; circular form. Multiple attacks; duration, forty-five years. Age at death, 74 years. Autopsy number, xvii-10.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	1—1	0	1—1	1—1	0
(4)	—	1—1	1—1	1—1	1—1
(5)	1—1	1—1	1·5—1	1·5—1	—
(6)	1·5—1	1·5—1	1·5—1	2—1	1—1

Case 5.—Maniacal depressive insanity; maniacal form. First attack; duration, five and a half years. Age at death, 35 years. Autopsy number, xvii-17.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	0	0	0	0	0
(4)	—	1—1	—	0	0
(5)	1—1	1—1	1—1	1—1	—
(6)	1·5—1	1·5—1	1·5—1	1—1	1·5—1

Case 6.—Maniacal depressive insanity; maniacal form. First attack; duration, two months. Age at death, 41 years. Autopsy number, xvii-32.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	0	0	0	0	0
(4)	—	0	—	0	0
(5)	1—1	1—1	1—1	0	0
(6)	1—1	1—1	1·5—1	1—1	1—1

Case 7.—Maniacal depressive insanity; maniacal form. Sixth attack; duration, thirty-one years. Age at death, 66 years. Autopsy number, xvii-48.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	0	0	1—1	0	0
(4)	—	1—1	1—1	0	1—1
(5)	1—1	1—1	1—1	1—1	—
(6)	1—1	1—1	1·5—1	1—1	1—1

Case 8.—Maniacal depressive insanity; depressed form. First attack; duration, five years. Age at death, 41 years. Autopsy number, xvii-49.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	0	0	0	0	0
(4)	—	1—1	—	0	1—1
(5)	1—1	1—1	1—1	1—1	1—1
(6)	1—1	1—1	1·5—1	1—1	1·5—1

Case 9.—Maniacal depressive insanity; maniacal form. Third attack; duration, seventeen years. Age at death, 70 years. Autopsy number, xvii-59.

	PCl.	PoCl	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	1—1	0	0	1—1	0
(4)	—	0	—	0	0
(5)	1·5—1	1—1	1—1	1—1	—
(6)	1·5—1	1—1	1·5—1	1·5—1	1—1

Case 10.—Maniacal depressive insanity; maniacal form (some depressions). Eleventh attack; duration, thirty-one years. Age at death, 75 years. Autopsy number, xiii-12.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	1—1	1—1	0	0	0
(4)	—	1—1	—	1—1	1—1
(5)	1—1	1—1	1—1	1—1	1—1
(6)	1·5—1	1·5—1	1—1	1·5—1	1·5—1

II.—Dementia Præcox Group.

Case 1.—Hallucinatory type; slight deterioration. Duration, eight months. Age at death, 31 years. Autopsy number, xv-22.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	0	0	0	0	0
(4)	—	0	—	0	0
(5)	0	0	0	0	0
(6)	1·5—1	1·5—1	0	0	0

Case 2.—Dementia præcox; hebephrenic form. Duration, three years. Age at death, 45 years. Autopsy number, xv-58.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	0	0	0	0	0
(4)	—	0	0	0	0
(5)	0	0	0	0	—
(6)	0	0	0	0	0

Case 3.—Dementia præcox; paranoid form. Duration, seven years. Age at death, 52 years. Autopsy number, xv-58.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	0	0	0	0	0
(4)	—	0	0	0	0
(5)	0	0	0	0	—
(6)	0	0	0	0	0

Case 4.—Dementia præcox; paranoid form. Duration, thirty-one years. Age at death, 69 years. Autopsy number xv-67.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	0	0	0	0	0
(4)	—	0	1—1	0	0
(5)	1—1	1—1	0	0	—
(6)	1—1	1—1	2—1	1—1	1—1

Case 5.—Dementia præcox; katatonic form. Duration, three years. Age at death, 41 years. Autopsy number, xv-79.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	0	0	0	0	0
(4)	—	0	0	0	0
(5)	0	0	0	0	—
(6)	0	0	0	0	0

Case 6.—Dementia præcox; paranoid form. Duration, thirteen years. Age at death, 43 years. Autopsy number, xv-84.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	0	0	0	0	0
(4)	—	0	0	0	0
(5)	0	0	0	0	—
(6)	0	0	0	0	0

Case 7.—Dementia præcox; hebephrenic form. Duration, seven years. Age at death, 29 years. Autopsy number, xvi-37.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	0	0	0	0	0
(4)	—	0	0	0	0
(5)	0	0	0	0	—
(6)	0	1—1	1—1	1·5—1	0

Case 8.—Dementia præcox; paranoid form. Duration, forty-six years. Age at death, 83 years. Autopsy number, xvii-4.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	1—1	0	0	1—1	1—1
(4)	—	0	0	1—1	1—1
(5)	1—1	1—1	1—1	1·5—1	—
(6)	1·5—1	1·5—1	1·5—1	1·5—1	1·5—1

Case 9.—Dementia præcox; hebephrenic form. Duration, twenty-eight years. Age at death, 63 years. Autopsy number, xvii-14.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	0	0	0	0	0
(4)	—	0	—	0	0
(5)	0	0	0	0	0
(6)	1—1	1—1	1—1	1—1	1·5—1

Case 10.—Dementia præcox; katatonic form. Duration, twenty-five years. Age at death, 60 years. Autopsy number, xvii-16.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	0	0	0	0	0
(4)	—	0	—	0	0
(5)	0	0	0	0	0
(6)	0	0	1·5 –1	1–1	1—1

III.—SENILE GROUP.

Case 1.—Senile dementia. Duration, six months. Age at death, 74 years. Autopsy number, xv-17.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	0	0	0	0	0
(4)	—	1—1	0	0	0
(5)	1·5—1	1—1	1—1	1—1	—
(6)	1·5—1	1·5—1	2—1	1·5—1	1—1

Case 2.—Senile dementia. Duration, nine years. Age at death, 73 years. Autopsy number, xv-18.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	1—1	0	1—1	0	1—1
(4)	—	0	1—1	0	1—1
(5)	1—1	1—1	1·5—1	1—1	—
(6)	1·5—1	1·5—1	2—1	1—1	1·5—1

Case 3.—Senile dementia. Duration, nine months. Age at death, 75 years. Autopsy number, xv-20.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	0	0	0	0	0
(4)	—	1—1	1—1	1—1	0
(5)	1—1	1—1	1–1	1—1	1—1
(6)	1—1	1·5—1	1·5 –1	1·5—1	1—1

Case 4.—Senile dementia. Duration, one month. Age at death, 75 years. Autopsy number, xv-25.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	1—1	1—1	1—1	1—1	1—1
(4)	—	1—1	1—1	1—1	1—1
(5)	1·5—1	1—1	1—1	1·5—1	1·5—1
(6)	2—1	1·5—1	2—1	2—1	2—1

Case 5.—Senile dementia. Duration, five months. Age at death, 76 years. Autopsy number, xv-29.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	0	0	0	0	0
(4)	—	0	—	0	
(5)	0	0	0	1—1	0
(6)	1—1	1—1	1—1	1—1	1—1

Case 6.—Senile paranoid condition. Duration, twenty-five years. Age at death, 83 years. Autopsy number, xv-40.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	1—1	0	0	0	0
(4)	—	1—1	0	0	0
(5)	1—1	1—1	1—1	0	0
(6)	1·5—1	1—1	1—1	1—1	1—1

Case 7.—Senile paranoid condition, with dementia. Duration, ten years. Age at death, 78 years. Autopsy number, xv-42.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	1—1	1—1	1—1	0	0
(4)	—	1—1	1—1	0	1—1
(5)	1—1	1·5—1	1—1	1—1	—
(6)	1·5—1	1·5—1	1·5—1	1·5—1	1—1

Case 8.—Senile paranoid condition. Duration, two years and a half. Age at death, 67 years. Autopsy number, xv-43.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	1—1	0	0	0	
(4)	—	1—1	1—1	0	0
(5)	1·5—1	1—1	1—1	1—1	—
(6)	2—1	1—1	1·5—1	1·5—1	1—1

Case 9.—Senile dementia. Duration, one month. Age at death, 62 years. Autopsy number, xv-57.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	0	0	0	0	0
(4)	—	0	0	0	0
(5)	1—1	0	1—1	0	0
(6)	1—1	1—1	1—1	0	0

Case 10.—Senile dementia. Duration, nine years. Age at death, 84 years. Autopsy number, xvi-2.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	0	0	0	0	0
(4)	—	0	0	0	0
(5)	0	0	0	0	0
(6)	1—1	1—1	0	1—1	0

IV.—General Paralysis Group.

Case 1.—General paralysis; demented. One year's duration (?). Age at death, 37 years. Autopsy number, xv-24.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	0	0	0	0	0
(4)	—	0	1—1	0	0
(5)	1—1	1—1	1—1	1—1	—
(6)	1·5—1	2—1	1·5—1	2—1	1—1

Case 2.—General paralysis; demented. Three years' duration. Age at death, 63 years. Autopsy number, xv-31.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	*	*	*	*	0
(3)	*	*	*	*	0
(4)	—	*	*	*	1—1
(5)	1·5—1	*	1—1	1—1	—
(6)	2—1	2—1	1·5—1	1·5—1	1—1

* Marked stratigraphic disturbance due to the lesions of general paralysis.

Case 3.—General paralysis. Four years' duration. Age at death, 43 years. Autopsy number, xv-33.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	0	0	0	0	0
(4)	—	1—1	1—1	0	0
(5)	1—1	1—1	1—1	1—1	1—1
(6)	1·5—1	1·5—1	1·5—1	1—1	1—1

Case 4.—General paralysis. Two years' duration. Age at death, 42 years. Autopsy number, xv-34.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	1—1	*	*	0	0
(4)	—	*	*	0	0
(5)	1—1	*	*	1—1	—
(6)	1·5—1	2—1	1·5—1	1—1	1—1

* Marked stratigraphic disturbance due to the lesions of general paralysis.

Case 5.—General paralysis. Two years' duration. Age at death, 54 years. Autopsy number, xv-41.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	1—1	1—1	1—1	0	0
(4)	—	1—1	1—1	0	0
(5)	1·5—1	1·5—1	1·5—1	1—1	1—1
(6)	2—1	1·5—1	1·5—1	1·5—1	1—1

Case 6.—General paralysis. One and a half years' duration. Age at death, 55 years. Autopsy number, xv-47.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	1—1	0	0	0	0
(4)	—	1—1	—	0	1—1
(5)	1—1	0	1—1	1—1	—
(6)	1·5—1	1·5—1	1·5—1	1—1	1—1

Case 7.—General paralysis. Six months' duration (?). Age at death, 36 years. Autopsy number, xvi-9.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	0	0	0	0	0
(4)	—	0	—	0	0
(5)	1—1	1—1	1—1	1—1	0
(6)	1·5—1	1—1	1·5—1	1—1	1—1

Case 8.—General paralysis. One year's duration. Age at death, 60 years. Autopsy number, xvi-14.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	1—1	0	0	0	0
(4)	—	0	—	0	0
(5)	1—1	1—1	0	0	0
(6)	1·5—1	1—1	1—1	0	0

Case 9.—General paralysis. Seven years' duration. Age at death, 49 years. Autopsy number, xvi-15.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	1—1	1—1	1—1	0	0
(4)	—	1—1	1—1	0	0
(5)	1—1	1—1	1·5—1	1—1	0
(6)	1·5—1	1·5—1	1·5—1	1·5—1	0

Case 10.—General paralysis. Two years' duration. Age at death, 40 years. Autopsy number, xvi-26.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0		0	0	0
(3)	1—1	1—1	0	0	0
(4)	—	1—1	1—1	0	0
(5)	1·5—1	1·5—1	1—1	1—1	0
(6)	1·5—1	1·5—1	1·5—1	1—1	0

V.—Alcoholic Insanity Group.

Case 1.—Alcoholic deterioration. Duration, three years.[1] Age at death, 46 years. Autopsy number, xv-44.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	0	0	0	0	0
(4)	—	0	0	0	0
(5)	0	0	0	0	—
(6)	1—1	1—1	1—1	0	0

Case 2.—Alcoholic deterioration. Duration, five years. Age at death, 61 years. Autopsy number, xv-45.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	0		0	0	
(4)	—	0	—	0	0
(5)	1—1	1—1	0	0	0
(6)	1—1	1—1	1—1	0	0

Case 3.—Alcoholic paranoid condition. Duration, nine years. Age at death, 37 years. Autopsy number, xv-73.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	1—1	0	0	0	0
(4)	—	0	0	0	
(5)	1—1	1—1	1—1	1—1	—
(6)	1·5—1	1·5—1	1·5—1	1·5—1	1—1

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[1] In the alcoholic group duration refers to duration of the psychosis, not the habit.

Case 4.—Alcoholic deterioration. Duration, sixteen years. Age at death, 58 years. Autopsy number, xvi-16.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	0	0	0	0	0
(4)	—	0	0	0	0
(5)	0	0	0	0	1—1
(6)	0	0	1—1	0	1—1

Case 5.—Alcoholic paranoid condition. Duration, one month. Age at death, 61 years. Autopsy number, xvi-19.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	1—1	0	1—1	0	0
(4)	—	1—1	—	0	0
(5)	1·5—1	1—1	1·5—1	1—1	1—1
(6)	2—1	1—1	1·5—1	1·5—1	1—1

Case 6.—Alcoholic deterioration. Duration, one month. Age at death, 65 years. Autopsy number, xvi-32.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	1—1	1—1	1—1	1—1	0
(4)	—	1—1	—	1—1	1—1
(5)	1·5—1	1·5—1	1—1	1—1	—
(6)	2—1	1·5—1	1·5—1	1·5—1	1—1

Case 7.—Alcoholic deterioration. Duration, six months. Age at death, 68 years. Autopsy number, xvii-13.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	1—1	1—1	1—1	1—1	1—1
(4)	—	1—1	1—1	1—1	1—1
(5)	1—1	1—1	1—1	1—1	1—1
(6)	1·5—1	1·5—1	1—1	1·5—1	1·5—1

Case 8.—Korsakow psychosis. Duration, ten years. Age at death, 57 years. Autopsy number, xvii-28.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	0	0	0	0	0
(4)	—	1—1	—	0	0
(5)	1—1	1—1	1—1	1—1	0
(6)	1—1	1—1	1·5—1	1·-1	1—1

Case 9.—Delirium tremens. Duration, several days. Age at death, 42 years. Autopsy number, xvii-33.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	0	0	0	0	0
(4)	—	1—1	—	0	0
(5)	1—1	1—1	1—1	1—1	0
(6)	1—1	1·5—1	1·5—1	1—1	1—1

Case 10.—Alcoholic deterioration. Duration, two years. Age at death, 61 years. Autopsy number, xvii-38.

	PCl.	PoCl.	F.	T.	Occ.
(1)	—	—	—	—	—
(2)	0	0	0	0	0
(3)	1—1	1—1	0	0	0
(4)	—	0	—	0	0
(5)	1—1	1—1	1—1	1—1	0
(6)	1·5—1	1—1	1—1	1—1	1—1

Analysis and Discussion.

In order to enable the more ready interpretation of the foregoing data in analytical form it has been deemed advisable to reduce the tables to a figure which will indicate at once the relative severity of reaction both in regard to the number of laminæ involved and the grade of involvement in each. This figure, which for convenience will be called the satellite index, is made up by counting the number of layers involved, giving each at the same time a value equivalent to the satellite—nerve-cell ratio. Thus the post-central cortex of Case I, 1, shows three laminæ with a count of 1 to 1 and one of 1·5 to 1, giving a satellite index of 4·5, while the frontal cortex of the same case has two laminæ with 1 to 1 reaction, and one each of 1·5 to 1 and 2 to 1, giving an index of 5·5. In all cases where a layer is wanting, e.g., precentral stellate, the interpretation has been made on the basis of the layer immediately above. That is the occurrence of a 1 to 1 reaction in the lamina ganglionaris is taken as evidence of an extension of the process above the position which a stellate layer would occupy and is considered as though a similar reaction occurred there. These methods of analysis are of course open to some question, but they will probably indicate the conditions within reasonable limits of error.

The records all tend to show a marked predilection for the deeper cell layers. Almost without exception the numerical record shows slight, if any, reaction in the upper laminæ, but a marked tendency to an increasing ratio as one after another of the subjacent laminæ is reached. Not only does the reaction tend to increase as one passes to the deeper layers, but even within one layer there may be a noticeable difference at various levels. Thus the deeper portions of the lamina pyramidalis and the lamina multiformis contain a noticeably larger number of satellites in the majority of instances than the upper levels. (This has been taken into account in the record of findings as mentioned above.) No attempt has been made to estimate the number of cells of the neuroglia type in the subcortical white matter, but the survey has given rise to a strong impression that those cases showing marked satellitosis also show an increase here.

An analysis of the satellite indices by laminæ of the whole series gives the following results :—

Lamina	Total indices (50 cases)	Average index
Granularis externa (2)	0	0
Pyramidalis (3)	59	1·18
Granularis interna (4)	88	1·76
Ganglionaris (5)	171·5	3·43
Multiformis (6)	276·5	5·53

The increase on reaching successively deeper layers is strikingly shown.

There is also a fairly constant tendency toward milder involvement of the occipital and temporal regions, as is shown by the following table :—

Region	Total indices (50 cases)	Average index
Precentral	149·5	2·99
Postcentral	131·5	2·63
Frontal[1]	132·0	2·64
Temporal	102·5	2·05
Occipital[2]	79·5	1·59

[1] Eighteen of the fifty cases represent a-granular frontal or cortex of the effector type.
[2] Twenty-three of the fifty cases are calcarine cortex.

In this table it must be considered that the inclusion of ten cases of general paralysis in which the severest expression is usually prerolandic or involves the pre-rolandic and post-central fields might play some part, but a similar analysis of the averages with the general paralysis series omitted has yielded about the same result.

The analysis by groups of psychoses has been carried out in a slightly different manner. In order to simplify the interpretation the cases have been separated into five groups, viz., (1) negative, those with a satellite count less than the nerve-cell count in all laminæ; (2) slight, where the satellite index was below 5; (3) moderate, with a satellite index between 5·5 and 10; (4) marked between 10·5 and 15; and (5) intense with an index above 15·5. This arrangement has yielded the following result:—

	Negative	Slight	Moderate	Marked	Intense
Maniacal depressive ...	0	0	1	4	5
Dementia præcox ...	4	4	2	0	1
Senile psychoses ...	0	2	1	4	3
General paralysis ...	0	0	2	6	2
Alcoholic psychoses ...	0	3	0	4	3

The most striking results of this analysis are the relation of the maniacal depressive and dementia præcox groups.

The first group, that of the maniacal depressive series, shows a marked tendency towards high indices, with one case in the moderate column and all of the remainder either marked or intense, while the dementia præcox group, in sharp contrast, shows fairly consistent low indices. This condition in dementia præcox stands in sharp contrast to the active neuroglia reaction (amœboid neuroglia and neurophagocytosis), which Alzheimer and others have shown in the active stages of the disease, but these changes are probably evanescent and would not be expected to play an important rôle in a series of cases such as the present, which are for the most part of long standing. Alzheimer emphasizes that the degree of these changes is in relation to the severity of the attack rather than its clinical expression, and that soon after an acute catatonic "storm," for instance, little of this sort of alteration may be demonstrable. In none of the other three groups were there cases of entirely negative count, but otherwise the distribution is more general.

In the one case of moderate reaction of the maniacal depressive group (Case I, 6) the patient died at the age of 41, while the patient with dementia præcox with an intense reaction lived to be 83. To control the influence of age the data have been arranged in a table by decades with the following result:—

	Negative	Slight	Moderate	Marked	Intense
Under 30	0	1	0	0	0
31—40	0	1	1	5	0
41—50	3	1	1	3	1
51—60	1	2	1	2	1
61—70	0	2	2	5	6
71—80	0	0	1	2	5
Over 81	0	1	0	1	1

This table seems to indicate a tendency for the more intense reactions to occur in the latter decades, but that age is not the only factor may be seen from Case III, 10, a senile dement, aged 84, with a satellite index of 3, which places it in the slight group.

Finally, the data have been rearranged to determine any possible relation between the duration of the psychosis and the degree of reaction. This is manifestly a difficult task as the time of onset in many of the included cases is difficult to determine with accuracy. In the maniacal depressive group the duration has been reckoned from the onset of the first attack. In the alcoholics no attempt was made to estimate the period of the habit, but the figures are taken from the onset of mental symptoms sufficient to-result in hospital commitment. The table follows :—

	Negative	Slight	Moderate	Marked	Intense
Less than 1 year	0	2	3	3	4
1 to 5 years	2	1	1	8	2
5 to 10 years	1	3	0	4	3
Over 10 years	1	2	2	3	5

Here there seems to be no definite relationship. The marked and intense cases are distributed with relative evenness throughout the varying periods. The eight cases in the 1- to 5-year period in the marked column seems disproportionate, but this is accounted for by the occurrence here of six cases of general paralysis.

CONCLUSIONS.

The analysis of the relative numerical occurrence of satellite cells in ten cases, each of five psychoses, seem to warrant the conclusion that satellitosis cannot be considered in any sense indicative of the type of psychosis, although it has in this series appeared with more consistent intensity in the maniacal depressive cases and has been of very much less prominence in dementia præcox.

The reaction elects the deeper cell layers both in regard to frequence of occurrence and degree of reaction.

The cortices of the dome, precentral, postcentral and frontal, seem to show the reaction with greater intensity than do the temporal and occipital regions.

Age at the time of death seems to play some part in the occurrence of severe reactions, but cannot be considered the only factor.

The duration of the psychosis bears no demonstrable relation to satellitosis.

BIBLIOGRAPHY.

[1] Alzheimer. *Zeitschr. f. d. Gesamte Neurol. u. Psychol.*, 1911, Bd., iv, S. 356.
[2] Berkley, H. J. *Philadelphia Med. News*, 1883, vol. xliii, p. 200.
[3] Clarke, J. M. *Brain*, 1897, vol. xx, p. 22.
[4] Collins, J. *Amer. Journ. Med. Sci.*, 1898, vol. cxvi, p. 275.
[5] Facklam, F. C. *Arch. f. Psychiat.*, 1898, Bd. xxx, S. 137.
[6] Greppin, L. *Arch. f. Psychiat.*, 1892, Bd. xxiv, S. 155.
[7] Kattwinkel. *Deutsche Arch. f. klin. Med.*, 1899, Bd. lxvi, S. 517.
[8] Kölpin. *Journ. f. Psychol. u. Neurol.*, 1908-9, Bd. xii, S. 57.
[9] Lannois, M., and Paviot, J. "Neurographs," 1908, vol. i, No. 2, p. 105.
[10] Margulis, M. S. *Journ. nervopat. i psikhiat*, Korsakova, 1910, Bd. x, S. 1191.
[11] Menzies, W. F. *Journ. Ment. Sci.*, 1892, vol. xxxviii, p. 560; *ibid.*, 1893, vol. xxxix, p. 50.
[12] Modena. *Annuario del Manicomio prov. di Ancona*, 1905.
[13] Monnier. *Thèse de Paris*, 1911.
[14] Oppenheim, H., und Hoppe, H. H. *Arch. f. Psychiat.*, 1893, Bd. xxv, S. 617.
[15] Raecke. *Arch. f. Psychiat.*, 1910, Bd. xlvi, S. 727.
[16] Rusk, G. Y. *Amer. Journ. Insan.*, 1902-03, vol. lix, p. 63.
[17] Schulz. *Charité-Annalen*, 1908, Bd. xxxii, S. 189.
[18] Stier, E. *Arch. f. Psychiat.*, 1903, Bd. xxxvii, S. 62.
[19] Weidenhammer. *Neurol. Cenralbl.*, 1901, Bd. xx, S. 1161.
[20] Wollenberg, R. "Nothnagel's Specielle Path. u. Therapie," 1899, Bd. xii, Teil II, Abt. 3.

PUBLICATIONS RECENTLY RECEIVED.

[*Notes on a Book under this heading do not preclude a subsequent review.*]

Die agrammatischen Sprachstörungen, Studien zur psychologischen Grundlegung der Aphasielehre. Von Professor Dr. ARNOLD PICK. Theil i. S. 291. Berlin: Springer, 1913.

The genius of Hughlings-Jackson was of the sort which comes to fruition through the minds of others; those who have been subject to its influence become dissatisfied with the idols of the market-place. The author of this monograph, of which the first part only has so far appeared, is probably the profoundest living student of Hughlings-Jackson's ideas, and his work is a plea for a more modern treatment of the question of Aphasia. For, although psychology is advancing rapidly, these disturbances of speech are still treated as a matter of cerebral "localization"; we hear of "memory pictures deposited in cells" and similar meaningless fantasies. Interest is centred, not on the nature of the disturbance of speech in any particular patient, but on the "localization" of the cause, which is supposed to underlie its appearance. Consequently we know something of the gross anatomy and diagrammatic symptomatology of certain brain lesions, but nothing about the real nature of defects of speech. This book begins with a plea for clear thinking, and a clean slate. The doctrines of aphasia are crusted with obsolete psychology and false physiology. The author passes on to consider the nature of a sentence, how it is built up, and in how far it exhibits the "propositioning function." He deals with the means of expression in speech, the way from thought to expression, Wundt's "Gesammtvorstellung" and the question of internal speech. This is one of the most stimulating books in neurology we have come across for a long time, and should serve to sweep away those mists which obscure the coming of a more modern doctrine of the higher disturbances of speech. We shall await the appearance of the second part with the greatest interest, and trust it will be furnished with a complete index.

Sémiologie des Affections du Système Nerveux. Par J. DEJERINE, Professeur de Clinique des Maladies du Système Nerveux à la Faculté de Médecine de Paris. Pp. 1212, avec 560 figures et 3 planches. Paris: Manon, 1914.

More than ten years ago Dejerine wrote a "Sémiologie des affections du système nerveux" for Bonchard's "Traité de Pathologie générale," and the present work is called a Second Edition. But, as a matter of fact, it has been entirely re-written and brought up to date in a remarkable manner; we know of no account of the symptomatology of nervous disease which contains so many of the more recent additions to knowledge. The book is admirably arranged, clear and lucid in exposition and filled with many new and excellent diagrams. The relation between the complicated anatomy of the brain-stem and the symptoms produced by lesions at various points between the upper end of the spinal cord and the optic thalamus is particularly clearly exposed. Even those to whom the French language is not familiar should possess this book for the sake of its figures alone.

The Modern Treatment of Nervous and Mental Diseases. Edited by WILLIAM A. WHITE, M.D., and SMITH ELY JELLIFFE, M.D., 2 vols. Illustrated. Pp. 867 and 816. London: Kimpton, 1913.

The first volume of this interesting work is devoted to mental diseases and to the psychical aspect of affections of the nervous system. Each of the nineteen chapters has been handed over to an authority on the subject, and they are all eminently readable. We might, perhaps, single out the chapters on the Educational Treatment of the Feeble-minded (Dr. Goddard), on Immigration and the Mixture of Races (Dr. Salmon), on the Neuroses and Psychoneuroses (Dr. Ernest Jones), and on Maniacal Depressive Insanity (Dr. Farrar).

The second volume is of even greater interest to the neurologist. Mr. Sherren deals with the treatment of injuries of the peripheral nerves; Dr. Jelliffe has written a concise account of headaches and of the treatment of syphilitic diseases of the nervous system. A chapter on Aphasia and Apraxia has been contributed by Dr. S. A. K. Wilson, and Dr. Gordon Holmes deals with the optic thalamus, mid-brain and cerebellum. Surgery of the brain and spinal cord is in the hands of Dr. Halstead and Dr. Vaughan. Many of the chapters have excellent bibliographies and there is a good index.

Organic and Functional Nervous Diseases. By M. ALLEN STARR, M.D., &c. Fourth edition, thoroughly revised. Pp. 970, illustrated with 323 engravings in the text and 30 plates in colours and monochrome. New York and Philadelphia: Lea and Febiger, 1913.

This well-known text-book of nervous diseases has been revised and a good deal of new matter has been added, especially in those parts which deal with the psychoneuroses. But knowledge has advanced so rapidly in the last ten years that no simple revision can be adequate, however excellent a text-book may have been when first published. The effects produced by lesions of the cerebellum, brain-stem, optic thalamus and basal nuclei are given in a somewhat cursory manner. The description of aphasia and allied conditions and of syphilis of the nervous system and its relation to the Wassermann test will require further revision in the next edition.

Lehrbuch der Nervenkrankheiten. Von Professor Dr. H. OPPENHEIM. Sechste, wesentlich vermehrte und verbesserte Auflage. S. 1926, mit 523 Abbildungen im Text und auf 4 Tafeln. Berlin: Karger, 1913.

In essential features the present edition is unaltered. New references have been added and most chapters show additions, especially in the paragraphs in small print dealing with the work of some one observer. The literature has been brought up to date and the number of references to recent papers is remarkable.

The Psychoneuroses and their Treatment by Psychotherapy. By Professor DEJERINE and Dr. E. GAUCKLER. Authorized translation by SMITH ELY JELLIFFE, M.D. Pp. 395. Philadelphia and London: Lippincott, 1913.

This is a translation of the well-known work of Professor Dejerine and his assistant, Dr. Gauckler, which was noticed in BRAIN, vol. xxxiv, p. 535. The book is of such importance to all who have to deal with the psychoneuroses that we welcome an English translation for those who cannot read it in the original French. Such readers will have to be content with an adequate rendering of its contents, but will miss the enjoyment of the charming style of the original.

Modern Problems in Psychiatry. By ERNESTO LUGARO. Translated by DAVID ORR, M.D., and R. G. ROWS, M.D., with a foreword by Sir T. S. CLOUSTON, M.D. Pp. 305. Manchester: University Press, 1913.

This is an excellent translation of the Second Edition of Professor Lugaro's well-known book. Throughout the standpoint is that of cerebral pathology, and little stress is laid on the part played by psychical processes in mental disease; in fact, this work represents the views of the extreme physical school of alienists. It is well got up and extremely easy to read.

Psychanalysis. By A. A. BRILL, M.D. Pp. 337. Philadelphia and London: Saunders, 1913.

In this book the psychoneuroses are treated from the strictest Freudian aspect. It forms a clear statement of the views of the Vienna physician on obsessions, hysteria, dreams, the compulsion neuroses, the psychopathology of everyday life and wit, illustrated by many examples.

Writers of "Original Articles and Clinical Cases" are supplied free of charge with 50 copies reprinted in the form in which the paper stands in the pages of "Brain." If reprints are required in pamphlet form, with wrapper, title-page, &c., and re-numbered pages, they must be ordered, at the expense of the writers, from Messrs. BALE, SONS & DANIELSSON, Ltd., 83-91, Great Titchfield Street, London, W.

Members of the Neurological Section of the Royal Society of Medicine can obtain the Index of "Brain" for the Volumes I. to XXIII. inclusive, that is, from its commencement to the end of 1900, from Messrs. MACMILLAN & CO., Ltd., St. Martin's Street, London, W.C., at the price of 6s. 6d., post free.

To those who are not members of the Neurological Section of the Royal Society of Medicine the price is 8s. 6d. net, and the volume may be obtained through any bookseller.

EDITOR.

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